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THE DIAGNOSIS AND TREATMENT OF RENAL-ARTERY STENOSIS

BY

J. J. BROWN, M.B., B.Sc., M.R.C.P.
Lecturer in Medicine

K. OWEN, M.S., F.R.C.S.
Surgeon

W. S. PEART, M.D., F.R.C.P.
Professor of Medicine

J. I. S. ROBERTSON, M.B., B.Sc., M.R.C.P.
Lecturer in Medicine

AND

D. SUTTON, M.D., F.F.R., M.R.C.P., D.M.R.D.
Radiologist

St. Mary's Hospital, London

[WITH SPECIAL PLATE]

The importance of renal-artery stenosis has received emphasis from reports of the alleviation of hypertension by operations which correct a stenosis or remove the affected kidney (Howard *et al.*, 1954; Poutasse, 1956; DeCamp and Birchall, 1958; Owen, 1960; Robertson, 1960). This condition in man parallels experimental hypertension produced in animals by clamping the renal artery (Goldblatt *et al.*, 1934). Renal-artery stenosis is now being recognized with increasing frequency in patients with high blood-pressure, and strict diagnostic criteria must be applied if successful surgical treatment is to be achieved. The diagnosis of renal-artery stenosis based upon inadequate data is likely only to lead to therapeutic failure and to bring the surgical methods employed into disrepute. Certain patients with renal-artery lesions and severe hypertension may be greatly improved by appropriate surgical procedures. It is, however, important that overenthusiastic investigation and treatment shall not result in unnecessary morbidity. We therefore wish to define the diagnostic criteria which, in the light of our experience of this condition, we consider significant. This is an amplification of points made previously (Peart, 1959; Owen, 1959, 1960; Robertson, 1960). The present paper is based on a study of 22 patients in whom renal-artery disease was proved or strongly suspected. Of these, 11 were judged to be likely to benefit from operation (see Table I).

Incidence of Renal-artery Stenosis.—Since 1957 we have routinely performed renal arteriography, usually by the selective method, in patients with severe hypertension. Of 160 cases investigated in this way, a renal artery lesion was demonstrated in 10. In eight of the other cases reported here, renal artery narrowing was revealed at aortography performed for other reasons (usually iliac or aortic stenosis, or abdominal aneurysm). Though these figures give only an approximate indication of the incidence of renal-artery stenosis as a cause of hypertension, they show that it is not rare.

Clinical Features

Aetiology.—The wide variety of disorders which may lead to renal-artery stenosis has been reviewed by DeCamp and Birchall (1958). The most frequent cause of narrowing, however, is an atheromatous plaque, usually situated close to the origin of the artery. Case 18 of the present series is of particular interest as an example of Takayashu's disease (pulseless syndrome) with renal-artery involvement.

Age Incidence.—There is a tendency for renal-artery stenosis to be seen more commonly in the older age-groups, but the disease is found in younger patients, and DeCamp and Birchall (1958) have reported the case of a 9-months-old baby with stricture of the renal artery and severe hypertension. The ages of the patients of the present series ranged from 17 to 65.

Evidence of Widespread Arterial Disease.—Renal-artery stenosis is to be suspected particularly in those hypertensive patients with evidence of occlusive arterial disease elsewhere. Of the present series, seven patients gave a history of intermittent claudication, five had ischaemic heart disease, and three had suffered strokes. Narrowing of the renal artery was found in 5 out of 32 cases in which aortography was performed to demonstrate a lower aortic occlusion (Starer and Sutton, 1958). The mouth of the renal artery may be involved in an upward extension of an aortic thrombosis (Case 20 of the present series); alternatively, as in Case 6, separate atheromatous renal-artery narrowing may be present in addition to a lower aortic block. Coronary or cerebral arterial occlusion and intermittent claudication are, however, not rare in cases of hypertension in the absence of demonstrable renal-artery stenosis. Conversely, nine cases of the present series (Nos. 1, 3, 4, 9, 10, 11, 17, 19, and 22) had no evidence of arterial disease elsewhere at the time of presentation. Cases 4, 17, and 22 were free of symptoms and were found to have high blood-pressure on routine examination.

Family History.—Only occasionally have we elicited any relevant family history. However, the father of Case 19 and a brother of Case 7 had experienced intermittent claudication, and the father of Case 9 had had both legs amputated "because of gangrene."

Complete Occlusion of Renal Artery.—In this event (Case 19; Adams and Newman, 1958) the patient may

TABLE I—*Case Histories*

Bl. urea = Blood urea in mg./100 ml. Chol. = Serum cholesterol in mg./100 ml. Creat. = Creatinine concentration in mg. 100 ml. Ex. = Exudates. Glom. = Glomeruli. Haem. = Haemorrhages. In. = Inulin concentration in mg./100 ml. Na = Sodium concentration in mEq/litre. P.A.H. = P.A.H. concentration in mg./100 ml. Pap. = Bilateral papilloedema. Tub. at. = Tubular atrophy. Ur.Fl. = Urine-flow in ml. per minute. Ur.L.C. = Urine leucocyte excretion rate per hour. Vis.Detn. = Visual deterioration.

Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Divided Renal Studies	Aortogram	Pathological Findings	Results
1 Male 47	R. ren. art. sten. Jan. '59, thromboendarterectomy	Vis. Dc.n.; dyspnoea. B.P. 240/150. Fundi: Pap., Ex., Haem. Pressures: Aorta / Ren. Art. Before: 270/110 / 0 After: 150/80 / 150/80	Contrast R. > L.	R. / L. Ur.Fl. 0·17 / 4·5 Na 67 / 135 Creat. 82 / 12 P.A.H. 752 / 167 C.cr. 17 / 65 C. P.A.H. 40 / 234	*Selective Renal:* R. stenosis near origin	No proteinuria. Bl. urea = 40. Chol. = 193. Ur.L.C. = 593,000. *R. renal biopsy:* patchy loss prox. con. tub., Glom. basement memb. thickening. *L. renal biopsy:* Tubs. normal Occas. sclerosed glom. Hyalinization of arterioles	May '59, B.P. 150/90, fundi normal, full work. Feb. '60, B.P. 132/82
2 Male 45	L. ren. art. sten. Oct. '58, thromboendarterectomy. May '59, L. nephrectomy	1956, angina, B.P. 140/110. 1958, Vis. Detn., dyspnoea, B.P. 260/160. Fundi: Pap., Ex., Haem. Abdom. bruit. Pressures: Aorta / Ren. Art. Before: 200/150 / 150/120 After: 200/150 / 165/150	No I.V.P. Pyelogram during arteriogram showed equal contrast R. + L.	L. / R. Ur.Fl. 2·1 / 4·1 Na 50 / 60 Creat. 12 / 14 P.A.H. 180 / 236 C.cr. 32 / 71 C. P.A.H. 95 / 242	*Selective Renal:* L. ren. art. sten. near origin. Lower 1/3 of kidney supplied by separate artery	Proteinuria. Bl. urea = 35. Chol. = 310. Ur.L.C. = 500,000. *L. renal biopsy:* Upper pole, widespread tub. atrophy; glom. basement membrane thickening, vessels normal. Lower pole: glom. and tubs normal; vessels, medial hypert.	No fall in B.P. after thromboendarterectomy. No response to drugs. May '59, nephrectomy. Main ren. art. thrombosed. July '59, B.P. 150/90. Feb. '60, B.P. 150/90, fundi normal
3 Male 47	L. ren. art. sten. Dec. '59, thromboendarterectomy and splenorenal anastomosis	Nocturia. Headaches. Vis. Detn. B.P. 230/140. Abdom. bruit. Fundi: Ex., Haem. Pressures: Aorta / Ren. Art. Before: 112/82 / 0 After: 150/80 / 150/80	*After fluid restriction:* Calices on L. narrow. Contrast L. > R. *After water load:* R., no contrast. L. good contrast: calices wider	L. / R. Ur.Fl. 2·7 / 9·2 Na 10 / 30 In. 375 / 130 P.A.H. 133 / 44 C.in. 38 / 45 C. P.A.H. 153 / 172	*Selective Renal:* L. stenosis near origin	Proteinuria. Bl. urea = 44. Chol. = 280. Ur.L.C. = 360,000. *L. renal biopsy:* normal	Feb. '60, B.P. 140/90. May '60, B.P. 140/90, fundi normal
4 Male 40	R. ren. art. sten. Oct. '59, thromboendarterectomy and side-to-side anastomosis, ren. art. to aorta. Hypotensive drugs	Routine exam. '44, B.P. 120/75. '49, B.P. 145/85. '54, B.P. 180/100. '59, B.P. 240/140. Fundi normal. Abdom. bruit. Pressures: Aorta / Ren. Art. Before: 240/150 / 135/75 After: 215/110 / 190/110	Normal	R. / L. Ur.Fl. 1·0 / 3·1 Na 101 / 119 In. 1,982 / 915 P.A.H. 392 / 158 C.in. 58 / 85 C. P.A.H. 165 / 210	*Selective Renal:* R. sten. near origin. R. kidney smaller than L.	No proteinuria. Bl. urea = 35. Ur. L.C. = 130,000. *R. renal biopsy:* few sclerosed glom.; patchy loss prox. conv. tubules. *L. renal biopsy:* normal except hyalinization of arterioles	No fall in B.P. March '60, divided renal studies: R. / L. / Bl. Ur.Fl. 1·8 / 8·2 / 2·4 Na 90 / 91 / 100 In. 179 / 182 / 167 P.A.H. 58 / 50 / 39 ? Segmental ischaemia. On bretylium. B.P. 160/100
5 Male 54	Abdom. aneurysm. L. hydronephrosis. L. ren. art. sten. Oct. '59, aneurysm wired	20 yrs. Claudication. '59, B.P. 180/120. No abdom. bruit. Op. Oct. '59, abdom. aortic aneurysm with adherent L. ureter Pressures: Aorta / Ren. Art. Mean: 175 / 175	L., no contrast. R., normal. *Retrograde:* L., hydronephrosis. R. normal	L. / R. Ur.Fl. 1·3 / 2·0 Na 38 / 76 In. 105 / 94 P.A.H. 43 / 484 C. in. 14 / 75 C. P.A.H. 14 / 324	*High Aorta Puncture:* Aneurysm lower thoracic and abdom. aorta. Stenosis L. renal	No proteinuria. Bl. urea = 50. Chol. = 242. Ur.L.C. = 311,000. *L. renal biopsy:* periglom. fibrosis; extensive tubular atrophy; diffuse interstitial fibrosis; foci of lymphocytes	No change
6 Male 52	Lower aortic thrombosis. Upper L. ren. art. sten. Feb. '58, L. nephrectomy. Hypotensive drugs	Claudication from childhood. Dyspnoea 1 year. '58, B.P. 300/140. Fem. pulse delayed. Extensive collaterals. Abdom. bruit. Fundi: Haem., Pap.	L., no contrast. R. normal. *Retrograde:* Small L. kidney	Not performed	*Lumbar:* Aortic occlusion from inf. mes. to ÷common iliacs. Nephrogram lower 1/3 L. kidney only. L. kidney smaller than R.	No proteinuria. Bl. urea = 39. L. kidney = 62 g. Lower pole artery normal. Small arteries to upper 2/3. *Histology:* upper 2/3: Marked tub. atrophy. Glom. basement memb. thickening. Art. intimal. Thickening. Lower 1/3: tubules normal. Glom. and vessels as upper 2/3	No fall in B.P. On hypotensive drugs. Gradual rise in bl. urea = 100 (March '60). Fundi normal. B.P. (March '60) = 220/110
7 Male 59	Aorto-iliac stenosis. L. ren. art. sten.	'57, claudication, B.P. 230/120. '59, angina, abdom. bruit, fundi normal	Contrast L. > R. Delayed on L.	L. / R. / Bl. Ur.Fl. 0·7 / 7·0 / 3·4 Na 30 / 33 / 32 In. 393 / 224 / 284 P.A.H. 131 / 62 / 89	*Lumbar:* Irregularity lower abdom. aorta L. ren. art. sten.	No proteinuria. Bl. urea = 33. Chol. = 235	March '60, unchanged, no treatment, B.P. 150/90
8 Male 65	Ret. art. occlusion. Ischaemic R. kidney. Hypotensive drugs	'58, thrombosis R. cent. ret. art. '59, C.V.A. (dysarthria, ataxia). B.P. 190/120. No abdom. bruit. Fundi: R. optic atrophy L. normal	Contrast R. > L. R. smaller than L.	R. / L. Ur. Fl. 1·2 / 3·9 Na 29 / 39 In. 898 / 326 P.A.H. 280 / 90 C.in. 29 / 33 C. P.A.H. 128 / 150	*High Aortic Puncture:* Irreg. dilated aorta. No ren. art. sten.	No proteinuria. Bl. urea = 33. Chol. = 150. Ur.L.C. 23,000	March '60, on hypotensive drugs. B.P. 180/100

TABLE I *(Continued)*

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Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Divided Renal Studies	Aortogram	Pathological Findings	Results
9 Female 40	"Hypertensive encephalopathy" L. ren. art. aneurysm and stenosis lower polar artery. Hypotensive drugs	'50, hypertension during pregnancy. *Dec.* '59, epileptiform fits. B.P. 250/160, fundi: few haem. Abdom. bruit. *March* '60, Opn. L. ren. art. aneurysm. Atheroma main branches. Stenosis lower polar artery Pressures: Aorta 125/105; Aneurysm 125/105 *Lower polar artery* 100/95	Normal	L. R. Bl. Ur.Fl. 2·1 3·8 4·6 Na 92 96 95 In. 384 193 285 P.A.H. 104 83 75	*Selective Renal:* Aneurysm left main ren. art. Sten. lower polar branch	No proteinuria. Bl. urea = 27. Ur.L.C. = 208,000. *Biopsies:* Lower pole, gross atrophy prox. con. tubs.; glom. basement memb. thickening; some sclerosed glom. Upper pole, Tubs. normal, some sclerosed glom.	On guanethidine. May '60, B.P. 160/100
10 Female 49	L. ren. art. sten. End-to-end anastomosis, ren. art. to aorta. Hypotensive drugs	'54, B.P. "High." '58, epistaxes, dyspnoea, nocturia. B.P. 260/160 Abdom. bruit. Fundi: Pap., ex., haem. Oct. '58, Opn. end-to-side anastomosis, ren. art. to aorta. No pressure measurements	Contrast equal. R. kidney smaller than L.	R. Bl. Na 99 70 Creat. 53 48 Failed to catheterize L. ureter	*Catheter in Aorta:* L. ren. art. sten. near origin. R. ren. art. also narrow	Proteinuria. Bl. urea = 32. *L. renal Biopsy:* Glom.—some sclerosed tubs.—focal atrophy. prox. conv. Arterioles-fibrinoid necroses	No fall in B.P. Hypotensive drugs. March '60, fundi normal, B.P. 150/100
11 Female 40	R. ren. art. sten. May '59, R. nephrectomy	'59, headaches, dyspnoea, B.P. 230/130. Fundi: ex. Abdom. bruit. Pressure-drop aorta/ren. art. = 90 mm.Hg	Not available	R. Bl. Na 25 67 Failed to catheterize L. ureter	*High Aortic Puncture:* R. stenosis near origin. R. kidney smaller than L.	No proteinuria. Bl. urea = 45. Chol. = 227. R. kidney wt. = 110 g. Histology marked tub. atrophy. Periglom. fibrosis. *L. biopsy* normal	Nov. '59, B.P. 150/90
12 Male 54	Aneurysm abdom. aorta. L. ren. art. sten. Aug. '59, aneurysm wired	1 yr. attacks L. abdom. pain. B.P. 220/100. E.C.G., old ischaemia. No abdominal bruit. Pressures aorta and distal ren. art. equal	Normal	Not performed	*Catheter in Aorta:* Aneurysm lower abdom. aorta. ?stenosis origin. L. ren. art.	Proteinuria. Bl. urea = 36. *L. kidney biopsy:* mild tub. atrophy; some sclerosed glom.	Nov. '59, unchanged
13 Male 36	? Ischaemic L. kidney. Hypotensive drugs	'56, claudication, dyspnoea, bruit R. fem. No abdom. bruit. B.P. 220/140. Fundi normal	Normal	L. R. Ur.Fl. 0·5 1·4 Na 142 168 Creat. 62 35 P.A.H. 910 490 C.cr. 37 56 C.P.A.H. 135 199	*High Aortic Puncture:* Two arteries to L. kidney. No stenosis seen	Proteinuria. Bl. urea = 37. Chol. = 390. Ur.L.C. = 360,000	April '60, 170/92 B.P.
14 Male 28	Congenital malformation R. kidney and pyelonephritis. Sept. '59, R. nephrectomy	'51, B.P. 155/105. '59, B.P. 200/115. No symptoms. No abdom. bruit. Fundi normal. M.S.U. coliforms. Aorta renal art. pressures equal	R. kidney small. Contrast poor. L. kidney large	R. L. Ur.Fl. 0·4 1·1 Na 58 89 In. 573 900 P.A.H. 167 272 C.in. 9 45 C.P.A.H. 48 237	*Selective Renal:* R. sten. near origin. Small lobulated R. kidney	Proteinuria. Bl. urea = 38. Chol. = 200. R. kidney wt. = 37 g. Histology: congen. malformation and pyelonephritis. L. ren. biopsy normal. Dissection R. ren. art. —no stenosis	Nov. '59, B.P. 150/94
15 Male 60	Aorto-iliac thrombosis. R. ren. art. sten. No treatment	'58, claudication. B.P. 190/100. Bruit R. costovertebral angle. Fundi normal	Contrast R. > L. R. kidney small	R. L. Ur.Fl. 4·2 9·4 Na 42 57 In. 328 191 P.A.H. 151 91 C.in. 54 70 C.P.A.H. 186 257	*High Aortic Puncture:* Aortic occlusion just below R. ren. art. Sten. R. ren. art.	Bl. urea = 40. Chol. = 220	April '60, B.P. 190/100
16 Male 42	Angina. Gangrene R. foot. L. ren. art. sten. R. lumbar sympathectomy. R. A K amputation	'54, B.P. 190/100. '58, Angina and gangrene R. foot B.P. 190/100	Contrast L. > R. Calices L. Narrower than R.	L. R. Ur.Fl. 2·2 4·0 Na 18 27 In. 332 216 P.A.H. 145 100 C.in. 20 24 C.P.A.H. 111 138	*High Aortic Puncture:* Atheroma abdom. aorta, iliacs, femorals. L. ren. art. sten. near origin	Proteinuria. Bl. urea = 42. Chol. = 329. L. renal biopsy = focal cortical scarring, Tub. atrophy. Glom. normal	
17 Female 21	L. ren. art. sten. March '60, spleno-renal anastomosis	No symptoms. B.P. 165/100. Fundi normal. No abdominal bruit	Contrast L. > R. L. kidney smaller than R.	L. R. Bl. Ur.Fl. 3·0 3·3 4·0 Na 28 31 In. 315 237 P.A.H. 111 106 In more conc. samples Na on L. > R.	*Catheter in Aorta:* L. ren. art. stenosis	No proteinuria. Bl. urea = 28. Chol. = 180. *Renal biopsies:* L. many sclerosed glom. tub. atrophy. Foci of lymphocytes. R. normal	April '60. B.P. 130/80. Too early for assessment

TABLE I (*Continued*)

Pt.	Diagnosis and Treatment	Clinical Features	I.V.P.	Divided	Renal	Studies	Aortogram	Pathological Findings	Results
18 Female 17	Pulseless syndrome (Takayashu's disease). Ischaemic R. kidney. Anticoagulants	Greek Cypriot. '53, hemiplegia, blindness. Both car. R. subclavian and axillary pulses absent. Femorals present. No abdom. bruit. B.P. 190 110	Good contrast R.>L. R. smaller than L.	Ur.Fl. Na P.A.H.	R. 0·4 47 1,520	L. 0·7 95 745	*Thoracic*: Occlusion innomin. and both carotids. L. vertebral large. Lower abdom. aorta narrow. R. ren. art. narrow	No proteinuria. Bl. urea = 46. Chol. = 236. W.R. negative	Not known
19 Male 48	Thrombosed aneurysm L. ren. art. Jan. '55. L. nephrectomy. '60. Iliac art. stenosis. (Case reported by Adams and Newman, 1958)	June '54, sudden pain L. loin. B.P. 140 90. Fundi normal. Nov. '54, headaches. B.P. 220 140. Fundi: pap., ex., haem. '60, claudication	L. poor contrast. R. normal	Not performed	Not performed		Not performed	Proteinuria. Bl. urea = 34. Chol. = 334. W.R. negative. L. kidney grossly scarred. Thrombosed aneurysm L. ren. art. Some areas complete infarction. Some areas tub. atrophy with intact glom	Oct. '55, B.P. 120 80. Sept. '56, B.P. 120 80. May '60, B.P. 120 80
20 Male 39	Lower aortic occlusion. L. ren. art. sten. 1956. L. nephrectomy and lower aortic graft	'52, Claudication. B.P. 125 60. '55, headaches. B.P. 205 110. Fundi: few haem. Pressure measurements not made	Not performed	Not performed	Not performed		*High Aortic Puncture*: Complete block abdominal aorta just below renals. Stenosis L. ren. art. L. kidney smal	No proteinuria. Bl. urea = 25. Chol. = 200. L. kidney wt. = 145 g. Histology: patchy change with necrosis of many prox. conv. tubs.	March '60, B.P. 130 80. Fundi normal
21 Female 54	R. ren. art. sten. Ischaemic heart dis. Chronic bronchitis. No treatment	1958, chronic bronchitis. B.P. 230 130. Oct. '59, myocard. infarct. Fundi normal. abdominal bruit	Contrast. R.>L. R. calices narrower than L. R. kidney smaller	Ur.Fl. Na In. P.A.H. C.In. C.P.A.H. In more conc. samples R.>L.	R. 0·1 90 3,100 1,590 12 58	L. 1·0 153 900 490 37 184	*Lumbar*: R. ren. art. sten. near origin	No proteinuria. Bl. urea = 36. Chol. = 210	March '60, B.P. 130 80
22 Female 28	R. ren. art. sten.	'59, var. vein clinic. B.P. 240 140. No symptoms. Fundi normal. No abdominal bruit	Normal	Ur.Fl. Na In. P.A.H.	R. Unreliable 77 1,110 394	L. 123 324 95	*Catheter in Aorta*: Delay in filling R. ren. art. Probable R. sten.	Proteinuria. Bl. urea = 36. Ur.L.C. 29,000. *R. renal biopsy*: atrophy prox. con. tub. Some sclerosed glom. Periglom. fibrosis. Hyalinization arterioles	Waiting surgical exploration

develop pain in the loin due to partial infarction of the kidney. Fever and neutrophil leucocytosis may occur, and confusion with an attack of pyelonephritis is clearly possible.

Embolism of Renal Artery.—This can lead to severe hypertension reversible by nephrectomy or removal of the clot. The possibility of this occurrence must therefore be borne in mind if a likely source of emboli is known to be present (Prinzmetal *et al.*, 1942; Bourne, 1954).

Arterial Bruits.—Frequently we have found a systolic bruit arising in the stenosed artery. The murmur is usually, but not invariably, audible on clinical examination, and is often best heard near the centre of the abdomen, just above the umbilicus and to one or other side of the midline. Fig. A shows a phonograph record of the abdominal murmur in Case 9. Occasionally the murmur is not heard anteriorly, but is loud in the costovertebral angle (Case 15). In all cases submitted to operation the renal arterial origin of the bruit has been confirmed by direct auscultation. In several instances a palpable thrill has also been found in the affected vessel. The systolic murmur is usually abolished when the patency of the renal artery is restored. In Case 2 thromboendarterectomy was ineffective, and the abdominal murmur persisted after operation, to become inaudible when the artery thrombosed completely. Bruits over other arteries than the renal may, of course, be indicative of more widespread arterial disease.

Appearance of Fundus Oculi.—The hypertension in renal-artery stenosis may be in the benign or malignant phase, and the appearances of the fundus vary accordingly.

Polyuria.—The association of polyuria with narrowing of the renal artery and hypertension figures in five case reports (Øster, 1947; Deming, 1954; Margolin *et al.*, 1957; DeCamp and Birchall, 1958; Dollery *et al.*, 1959). Case 3 of the present series gave a history of nocturnal frequency of micturition in the three years before admission, though the significance of this remains doubtful. In hospital he showed neither frequency nor polyuria.

Potassium Loss and Hypokalaemia.—Dollery *et al.* (1959) reported two cases of renal-artery obstruction with hypertension, hypokalaemia, and urinary potassium loss. Unfortunately, ureteric catheterization studies failed technically. We have not encountered hypokalaemia in the present series; though in many of the cases with renal-artery stenosis we have compared urinary potassium output on the two sides, we have not observed excessive potassium excretion by either kidney.

Proteinuria.—This may or may not be present in renal-artery stenosis, and is usually unhelpful in diagnosis.

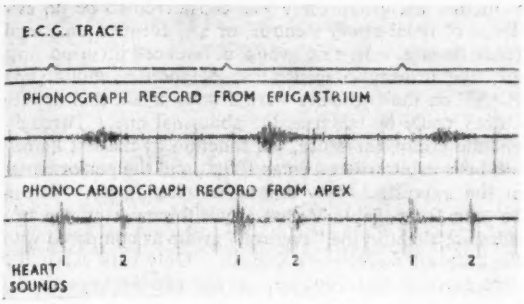

FIG. A.—Phonograph record of abdominal murmur in Case 9.

Urinary Cell-excretion Rate (Houghton and Pears, 1957).—Though most of our cases have had a moderately raised leucocyte excretion rate (up to 500,000/hour), this finding is not uncommon in several forms of hypertension, and does not appear to have particular relevance to renal-artery stenosis.

Special Investigations

Ureteric Catheterization Studies

It was shown by Mueller *et al.* (1951) that constriction of one renal artery in the dog resulted in a decrease in the volume and sodium concentration of the urine obtained from the kidney with the narrowed artery, as compared with the normal side. Howard *et al.* (1954) obtained similar results in a patient later shown at operation to have a stenosis of the main renal artery. Further studies of separate renal function in hypertension were reported by Connor *et al.* (1957, 1960). We have routinely carried out divided renal-function studies in patients with suspected renal-artery stenosis.

Method

Sodium pentobarbitone was used for premedication, and in order to ensure adequate flow of urine the patients were given 125–250 ml. of water to drink every 15 minutes during the hour preceding the investigation. Saddle-block spinal anaesthesia was induced by means of intrathecal dibucaine hydrochloride, and olivary-tipped ureteric catheters were passed via a cystoscope. The positions of the catheters were adjusted under radiographic control until the tips were judged to lie in the respective renal pelves. A self-retaining catheter was left in the bladder in order that any leak around the ureteric catheters immediately became apparent. When leakage occurred, the positions of the ureteric catheters were altered until the leak stopped or was reduced to a minimum. The water load was maintained throughout by oral replacement equal to urine volume. After usually two satisfactory urine collection periods had been obtained, 0.9% sodium chloride containing inulin and sodium *para*-amino-hippurate (P.A.H.) was infused at a constant rate into an arm vein. Further periods of urine collection were then taken after equilibration. Blood samples were withdrawn as required from an indwelling venous cannula in the opposite arm. In some patients, endogenous creatinine clearance was measured instead of inulin clearance. A course of nitrofurantoin or sulphonamide was given after the test.

In no case of the present series have we encountered urinary infection after ureteric catheterization, and, apart from occasional transient discomfort to the patient, the procedure has been free from complications. We would stress the importance of avoiding, if at all possible, any leakage around the ureteric catheters into the bladder. Only in this way can accurate measurements of urine flow and clearances be made. There is evidence (Levinsky and Berliner, 1959; Yendt *et al.*, 1960) that movements of water and electrolytes can take place across the walls of the ureter and bladder, and our experience confirms that calculations of the amount of leakage from either side based upon the relative concentrations of electrolytes in the ureteric samples and in the bladder are unreliable. Investigations where only one ureter is catheterized, the bladder urine being assumed to come entirely from the opposite side, are also open to question.

Ureteric Catheterization Findings in Renal-artery Stenosis

The kidney with the renal-artery stenosis forms a smaller volume of glomerular filtrate than the opposite kidney; further, a higher proportion of the filtered water, sodium, and chloride is reabsorbed on the affected side. Comparing the affected kidney with its fellow, therefore, the characteristic features of renal-artery stenosis on ureteric catheterization studies are, on the side with the lesion, diminished urine flow; lowered clearances of inulin, creatinine, and P.A.H.; increased urinary concentrations of inulin, creatinine, and P.A.H.; and, usually, diminished urinary concentrations of sodium and chloride. As Birchall *et al.* (1958) have pointed out, the final urinary concentration of sodium depends upon two variables, the tubular reabsorption of water and of sodium. It is therefore possible that the proportions of both the filtered water and the sodium reabsorbed on the side with the stenosis could exceed those on the normal side, and yet the final urinary concentration of sodium be higher on the former.

The higher urinary concentration of inulin and creatinine on the affected side in renal-artery stenosis has important implications in relation to intravenous pyelography and is further discussed later.

Findings in the Present Series

The results obtained in three proved cases of renal-artery stenosis (Nos. 1, 3, and 4) are shown in Tables II–IV. In each case the data relating to the affected kidney

TABLE II.—*Case* 1. *Stenosis Right Main Renal Artery*

	Period	R	L
Urine volume (ml./min.)	8	0·25	3·7
	9	0·17	4·5
	10	0·15	5·5
Sodium (mEq/l.)	8	45·0	100·0
	9	67·0	135·0
	10	115·0	144·0
Chloride (mEq/l.)	8	19·0	86·0
	9	32·0	123·0
	10	58·0	130·0
Urine P.A.H. concentration (mg./100 ml.)	9	752·0	167·0
	10	2,160·0	173·0
Urine creatinine concentration (mg./100 ml.)	9	81·6	12·4
	10	128·6	11·6
P.A.H. clearance (ml./min.)	9	40·0	234·0
	10	98·0	288·0
Creatinine clearance (ml./min.)	9	17·0	65·0
	10	23·0	70·0

are given first. In these patients, renal-artery stenosis was confirmed at operation, and a distinct pressure-drop across the site of the lesion was measured. In Table V a comparison is made of the normal with the affected kidney in these three cases with regard to urine-flow and the concentrations of sodium, P.A.H., and inulin or creatinine. In each instance the performance of the normal kidney is taken as 100%. In the second part of Table V similar data are presented for nine other cases (Nos. 7, 8, 13, 15, 16, 17, 18, 21, and 22) in which a diagnosis of renal-artery stenosis was regarded as probable, though not proved. For comparison, the findings in nine "control" cases, eight of which had hypertension, are given in the third part of the table.

TABLE III.—*Case 3. Stenosis Left Main Renal Artery*

	Period	L	R
Urine volume (ml./min.)	11	2·7	9·2
	12	2·0	9·0
	13	2·1	8·0
Sodium (mEq/l.)	11	10·0	30·0
	12	9·0	30·0
	13	6·0	22·5
Chloride (mEq/l.)	11	3·6	27·5
	12	3·5	29·4
	13	0·14	27·5
Urine P.A.H. concentration (mg./100 ml.)	11	133·0	44·0
	12	138·0	39·0
	13	153·0	45·0
Urine inulin concentration (mg./100 ml.)	11	375·0	130·0
	12	516·0	121·0
	13	420·0	134·0
P.A.H. clearance (ml./min.)	11	153·0	172·0
	12	118·0	148·0
	13	137·0	154·0
Inulin clearance (ml./min.)	11	38·0	45·0
	12	40·0	41·0
	13	33·0	40·0

TABLE IV.—*Case 4. Stenosis Right Main Renal Artery*

	Period	R	L
Urine volume (ml./min.)	14	1·0	3·1
	15	0·8	2·3
Sodium (mEq/l.)	14	101·0	119·0
	15	103·0	127·0
Chloride (mEq/l.)	14	90·0	119·0
	15	93·0	134·0
Urine P.A.H. concentration (mg./100 ml.)	14	392·0	158·0
	15	549·0	212·0
Urine inulin concentration (mg./100 ml.)	14	1,982·0	915·0
	15	1,215·0	1,012·0
P.A.H. clearance (ml./min.)	14	165·0	210·0
	15	196·0	215·0
Inulin clearance (ml./min.)	14	58·0	85·0
	15	36·0	85·0

TABLE V.—*Comparison of Normal With Affected Kidney*

	Urine Flow		Urinary Sodium		Urinary P.A.H.		Urinary Inulin or Creatinine	
	Range	Mean	Range	Mean	Range	Mean	Range	Mean
Proved renal-artery stenosis (3 cases)	−65 to −97	−80	−15 to −73	−46	+150 to +1,150	+357	+20 to +1,000	+354
Probable renal-artery stenosis (9 cases)	−45 to −96	−66	−45 to +20	−18	+4 to +1,900	+239	+33 to +870	+169
No unilateral renal disease (9 cases)	+24 to −41	−12	−9 to +10	−1	−36 to +50	+5	−37 to +50	0

The figures refer in the cases of renal artery stenosis to percentage variations in the function of the abnormal kidney, the function of the opposite kidney being taken as 100%. In the cases without unilateral renal disease the function of the left kidney has been arbitrarily taken as 100%.

In this last group there was considered to be no evidence of renal-artery stenosis, or any form of unilateral renal disease. In this group differences in urine flow and the urinary concentration of sodium, inulin, and P.A.H. on the two sides were always small, and neither kidney could be taken as the abnormal one. Throughout the group, therefore, the function of the left kidney has been arbitrarily taken as 100%, and the performance of the opposite kidney expressed accordingly. It can be seen from Table V that any differences on the two sides are slight in the "control" group as compared with the cases of renal-artery stenosis. Only very rarely did differences in the function of the two kidneys in the "control" group extend into the range of difference seen in the proved or probable cases of renal-artery stenosis. These occasions were usually isolated collection periods in the patients concerned; for the most part, differences between the two kidneys were well outside the range found in renal-artery stenosis.

More decisive is the pattern of disordered function seen in renal-artery stenosis. In all the probable and proved cases the affected kidney produced less urine, with a higher concentration of P.A.H., inulin, and creatinine, and almost invariably a lower concentration of sodium and chloride than its fellow. This pattern was never seen in the "control" group, where, if one kidney secreted less urine with a lower concentration of sodium than the other, a lower concentration of inulin and P.A.H. was also found on that side.

Variations in Urinary Sodium Concentration on the Two Sides

In none of the fully established cases of renal-artery stenosis in this series have we found, on divided function studies, deviations from the pattern set out above, except where these were associated with a lesion in a segmental artery. In two patients, however (Cases 17 and 21), in whom there was a probable though not finally proved renal-artery stenosis, occasional urine-collection periods showed higher sodium concentrations on the affected than on the unaffected side. In both of these cases the inulin and P.A.H. concentrations were persistently higher on the affected side. In Case 21 calculation showed that a higher proportion of the filtered water and sodium was reabsorbed on the suspect side, even where the final urinary sodium concentration was higher. Similar calculation was not possible in Case 17, since leakage around the ureteric catheters occurred, and the inulin clearance consequently could not be determined.

Birchall *et al.* (1958) reported a proved case of renal-artery stenosis in which ureteric catheterization studies showed persistently higher sodium concentration in the urine from the affected kidney. These workers similarly were able to show that a higher proportion of the filtered sodium and water was reabsorbed on the affected side. Connor *et al.* (1960) have criticized the findings of Birchall and his colleagues, suggesting that the infusion of saline containing inulin and P.A.H. may alter the pattern of electrolyte excretion on the two sides and invalidate the test. We have, as described above, taken samples both before and after starting such infusions, and have never found that the relative urine volumes or sodium concentrations are altered in these circumstances. The total quantity of sodium infused in the course of the test is in fact small, never being more than of the order of 50 mEq. The explanation of Connor *et al.* cannot in any event apply to the two patients in whom we found variations in the relative sodium concentrations

on the two sides, since these variations were found in collection periods taken both before and after the start of the infusion. We were, of course, not able to calculate the tubular reabsorption of sodium and water in the periods before the infusion of inulin, since we had in these no measure of the glomerular filtration rate.

For the present, we prefer to study the wider pattern of disordered function on the suspect side as revealed by the relative urine-flow rates, the inulin and P.A.H. clearances, and the concentrations of sodium, inulin, creatinine, and P.A.H., rather than relying simply on the comparative urine-flow rates and sodium concentrations. To what extent the altered excretory pattern we have described above is specific to renal-artery stenosis is not finally determined.

Cases with No Demonstrable Lesion in the Main Renal Arteries

In two instances (Cases 8 and 13) the divided studies were typical of renal-artery stenosis by our criteria, but arteriography demonstrated no lesion in the major renal arteries. It is possible that intrarenal arterial occlusion had occurred, but no such abnormality was revealed radiologically. These cases have not been subjected to operation, and at present are controlled by hypotensive drugs. They are included as cases of probable but not proved renal-artery stenosis in Table V.

Cases with a Lesion in a Segmental Artery

When the lesion occurs in a segmental artery the amount of renal tissue involved in the ischaemic process may be so small that any difference between the two kidneys as judged by ureteric catheterization studies is masked. This is well seen in Case 9 (Fig. 1, Special Plate; Table VI), in which an aneurysm with an irregular wall was found in the main left renal artery. At operation the pressures in the aorta and in the distal part of the main renal artery were equal at 125/105 mm. Hg; in the attenuated lower polar artery, however, the pressure was only 100/95 mm. Hg. Biopsy of the lower pole of the kidney showed evidence of ischaemia; the upper pole showed minor changes only.

Similar in some respects was Case 2 (Fig. 2, Special Plate; Table VII). This man had an atheromatous plaque at the mouth of the main left renal artery, but the lower pole of the kidney was supplied by a separate artery arising directly from the aorta. It is noteworthy here that, though the greater part of the left kidney was supplied by the affected vessel, the urinary creatinine and P.A.H. concentrations on the left were slightly lower than on the right. Histologically (Fig. 10) tubular damage here was considerable, and this might well have

TABLE VI.—*Case 9. Narrowing of Segmental Artery (Left)*

	Period	L	R	B*
Urine volume (ml. min.)	4	2·1	3·8	4·6
	5	2·2	2·3	5·0
	6	1·9	2·2	4·6
Sodium (mEq/l.)	4	92	96	95
	5	99	98	101
	6	108	106	109
Chloride (mEq/l.)	4	75	78	78
	5	85	86	85
	6	90	92	91
Urine P.A.H. concentration (mg./100 ml.)	4	101	82	75
	5	106	100	
	6	110	97	95
Inulin concentration (mg./100 ml.)	4	384	193	285
	5	343	239	356
	6	425	303	347

* B = bladder.

TABLE VII.—*Case 2. Stenosis Left Main Renal Artery. Aberrant Artery to Lower Pole*

	Period	L	R
Urine volume (ml. min.)	4	2·1	4·1
	5	1·5	2·3
Sodium (mEq/l.)	4	50·0	60·0
	5	66·0	75·0
Chloride (mEq/l.)	4	45·0	52·0
	5	55·0	62·0
Urine P.A.H. concentration (mg./100 ml.)	4	181·0	236·0
	5	334·0	377·0
Urine creatinine concentration (mg. 100 ml.)	4	12·0	14·0
	5	19·7	23·6
P.A.H. clearance (ml. min.)	4	94·0	242·0
	5	128·0	219·0
Creatinine clearance (ml. min.)	4	32·0	71·0
	5	41·0	71·0

contributed to the somewhat atypical results. These last two cases have not been included in Table V.

Because of the limitations of divided renal function studies in cases such as those described above, and also in bilateral renal-artery stenosis, some authors have questioned the value of these tests, preferring to rely for diagnosis mainly upon the angiographic appearances (Dustan *et al.*, 1959). Angiography may occasionally be misleading, however, and in such instances ureteric catheterization studies are of great value. Two patients of the present series illustrate this point.

In Case 5 (Fig. 3, Special Plate) aortography showed a lower aortic aneurysm and a narrowing of the left renal artery. Intravenous pyelography failed to demonstrate the left renal tract, and the patient was found to have a left-sided hydronephrosis, the ureter being distorted and obstructed by the aneurysm. Ureteric catheterization studies in this patient (Table VIII) were

TABLE VIII.—*Case 5. Left Hydronephrosis and Possible Left Renal-artery Stenosis*

	Period	L	R
Urine volume (ml./min.)	6	1·3	2·0
	7	2·0	5·0
Sodium (mEq/l.)	6	38·0	76·0
	7	38·0	87·0
Chloride (mEq/l.)	6	32·0	52·0
	7	34·0	60·0
Urine P.A.H. concentration (mg./100 ml.)	6	43·0	484·0
	7	45·0	473·0
Urine inulin concentration (mg./100 ml.)	6	105·0	94·0
	7	116·0	104·0
P.A.H. clearance (ml./min.)	6	14·0	324·0
	7	15·0	290·0
Inulin clearance (ml./min.)	6	4·0	75·0
	7	4·0	69·0

not those typical of renal-artery stenosis, in that, though the urine-flow rate and sodium concentration were lower on the left, there was little or no difference in the inulin concentration on the two sides, and the P.A.H. concentration was distinctly lower on the left. At operation no pressure-drop or alteration in the shape of the pulse wave was found distal to the site of the apparent lesion. In this instance the interpretation of the renal biopsy appearance was complicated by the presence of the hydronephrosis.

Ureteric catheterization studies were not typical of renal-artery stenosis also in Case 14 (Fig. 4, Special Plate; Table IX), where selective arteriography had suggested this diagnosis. Again, the inulin and P.A.H. concentrations were found to be lower on the affected

side. The arteriographic appearance here was later shown to be a radiological artifact (see below).

Lastly, it should be pointed out that the information provided by ureteric catheterization studies is of great value as a measure of the renal reserve, should nephrectomy rather than a reconstructive operation be contemplated.

These tests are tedious for both the patient and the investigator, and it is necessary to interpret the results with care. We have, however, found them to be generally the most reliable index of a renal arterial lesion.

TABLE IX.—*Case* 14. *Right Pseudostenosis*

	Period	R	L
Urine volume (ml./min.)	5	0·37	1·1
	6	0·37	0·8
Sodium (mEq/l.)	5	58·0	89·0
	6	75·0	111·0
Chloride (mEq/l.)	5	49·0	80·0
	6	67·0	99·0
Urine P.A.H. concentration (mg./100 ml.)	5	117·0	272·0
	6	208·0	333·0
Urine inulin concentration (mg./100 ml.)	5	573·0	900·0
	6	687·0	1,040·0
P.A.H. clearance (ml./min.)	5	48·0	237·0
	6	64·0	216·0
Inulin clearance (ml./min.)	5	9·0	45·0
	6	11·0	36·0

Plain X-ray Films

In many of the cases of renal-artery stenosis the affected kidney was found to be smaller than its fellow, though often the difference was not great enough to be helpful diagnostically. In two instances (Cases 3 and 22) there was no difference in length, and in Cases 4, 7, 15, 17, and 21 the affected kidney was shorter by less than the 1.5 cm. which Hodson (1957) regards as representing a significant difference in kidney size. It should also be borne in mind that in normal persons the right kidney may be appreciably smaller than the left (Moëll, 1956). In no patient of the present series was the unaffected kidney the smaller one. The greatest disparity in size was seen in the girl with Takayashu's disease (Case 18), where the respective lengths of the kidneys were 6.5 and 11.5 cm. Nevertheless, a better pyelogram was seen on the affected side here.

Intravenous Pyelography

This investigation has important implications in relation to renal-artery stenosis. The ureteric catheterization studies showed that renal-artery stenosis typically resulted in higher concentrations of inulin, creatinine, and P.A.H. in the urine from the affected side. The dyes currently employed in excretion urography—sodium acetrizoate and sodium diatrizoate are, in the usual doses, excreted mainly by glomerular filtration (Porporis *et al.*, 1954; McChesney and Hoppe, 1957), and the concentrations of radiopaque dye in the urine on the two sides will thus parallel the inulin and creatinine concentrations. It is to be anticipated, therefore, that renal-artery stenosis will be represented on intravenous pyelography by higher contrast and better visualization on the affected side than on the normal, provided that severe structural damage has not occurred in the kidney (Peart, 1959).

Better contrast on the side with the stenosis was, in fact, seen in seven cases of the present series (Nos. 1, 3, 15, 16, 17, 18, and 21) (See Fig. 5, Special Plate). This may falsely suggest impairment of function in the kidney with the normal renal artery, and there is a very real danger in these cases of the unaffected kidney being removed, with disastrous consequences. This misinterpretation is particularly likely to occur if for some reason dehydration before intravenous pyelography has been inadequate, with the result that the contrast on the side with the normal renal artery is poor. Case 3 affords a striking example of this.

This patient was a man with severe hypertension in whom intravenous pyelography performed at another hospital had shown poor contrast on the right side. It had been suggested, therefore, that there was a lesion of the right kidney, possibly responsible for the hypertension. Ureteric catheterization studies were, however, typical of a stenosis of the left renal artery (Table III), and this was confirmed by selective renal arteriography (Fig. 6, Special Plate). Intravenous pyelography was then repeated with the patient deliberately loaded with 500 ml. of water. This had the effect of obliterating the contrast on the normal side, though the kidney with the renal-artery stenosis was very clearly visualized (Fig. 7, Special Plate).

Several authors have commented on the preservation of the excretion pyelogram of a kidney with a stenosed artery, though the fact that better contrast may often be seen on this side seems to have passed unnoticed (DeCamp and Birchall, 1958; Page *et al.*, 1959; Squire and Schlegel, 1959; Yendt *et al.*, 1960). In consequence, the tendency has been to overstress the limitations of this technique. Several of the illustrations in the paper by Squire and Schlegel, for example, show greater pyelographic density on the side with the lesion, though the pictures are regarded by these authors as showing no abnormality. Intravenous pyelography is often, in fact, a most valuable diagnostic test in renal artery stenosis. Where bilateral renal-artery stenosis is present, particularly good contrast might be expected on excretion urography. The case described by Yendt *et al.* (1960) appears to be an example of this phenomenon.

In many cases an estimation of the rate of urine-flow on the two sides can be made by comparing the degree of filling of the pelvis and calices. Typically, on the side with the stenosis there will be less distension by urine, though contrast will be denser because of the comparatively high concentration of dye present. In some reports the calices have even been described as "spastic" on the affected side.

In those patients with severe renal structural damage (Cases 6 and 19) the pyelogram will, of course, be poor or absent on the side with the lesion, but these are the

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FIG. 1.—Selective renal arteriogram in Case 9, showing aneurysm sac and attenuated lower polar artery.

FIG. 2.—Selective renal arteriogram in Case 2. The artery demonstrated supplied only the upper two-thirds of the kidney.

FIG. 3.—Aortogram in Case 5, showing narrowing at origin of left renal artery.

FIG. 4.—Selective renal arteriogram in Case 14, showing small lobulated kidney and apparent renal-artery stenosis.

FIG. 5.—Intravenous pyelogram in Case 1 15 minutes after injection of the dye, showing better contrast on the side with the renal-artery stenosis.

FIG. 6.—Selective renal arteriogram in Case 3, showing stenosis at origin of left renal artery, with post-stenotic dilatation.

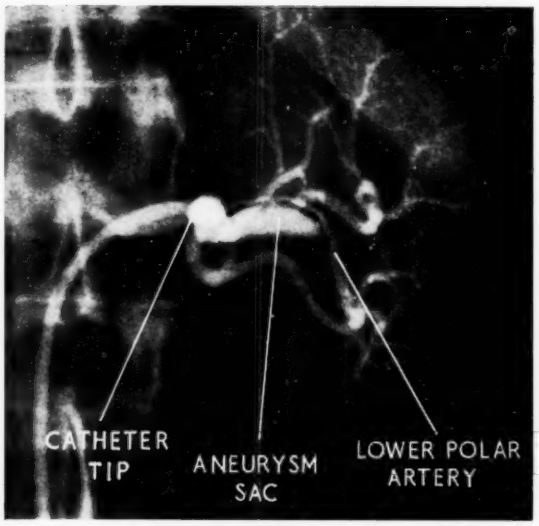


FIG. 1

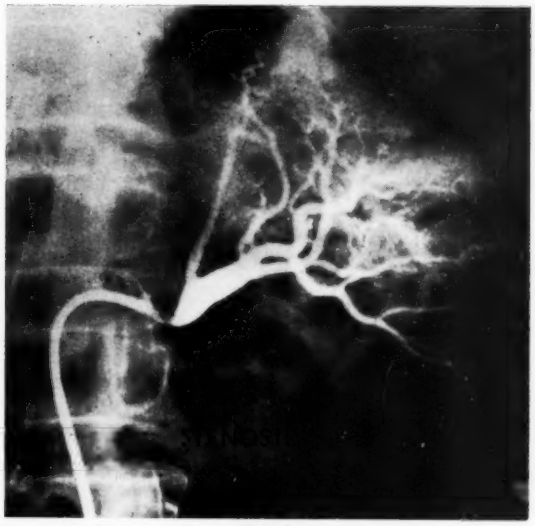


FIG. 2

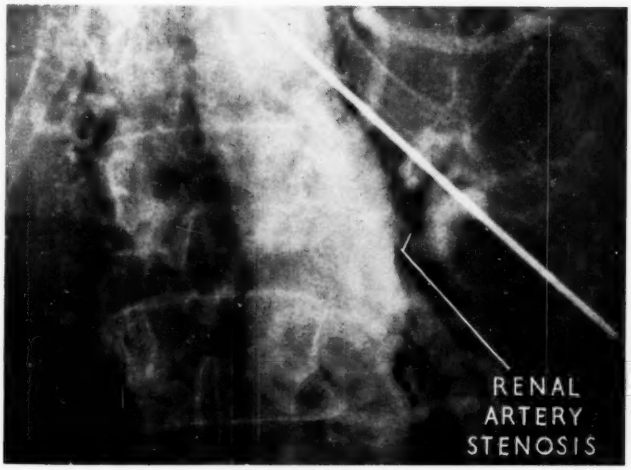


FIG. 3

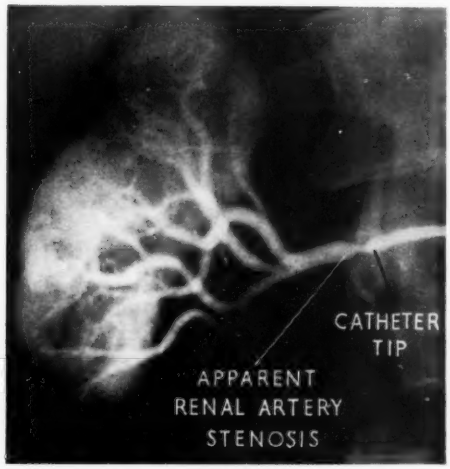


FIG. 4

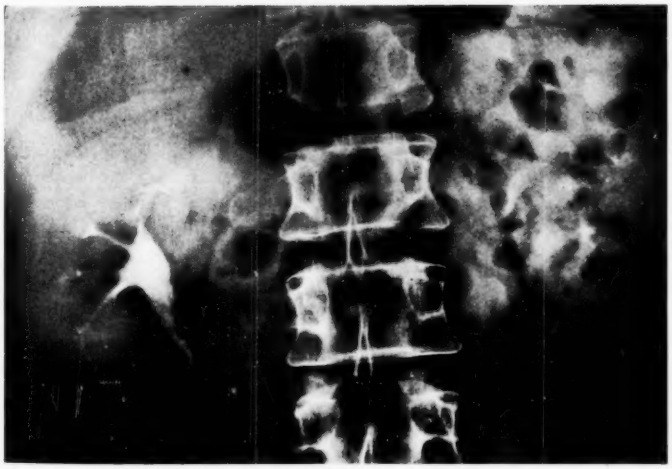


FIG. 5

FIG. 6

FIG. 7

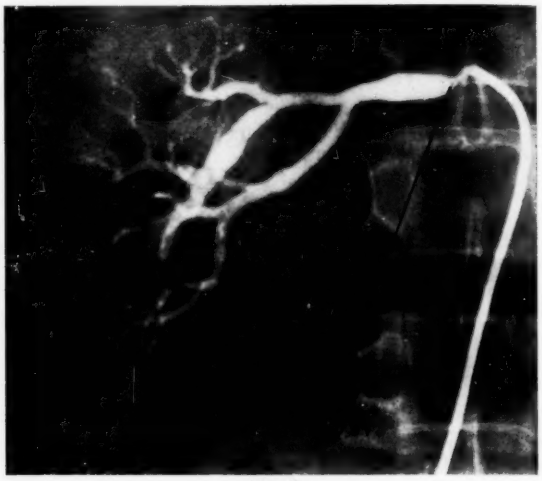


FIG. 8

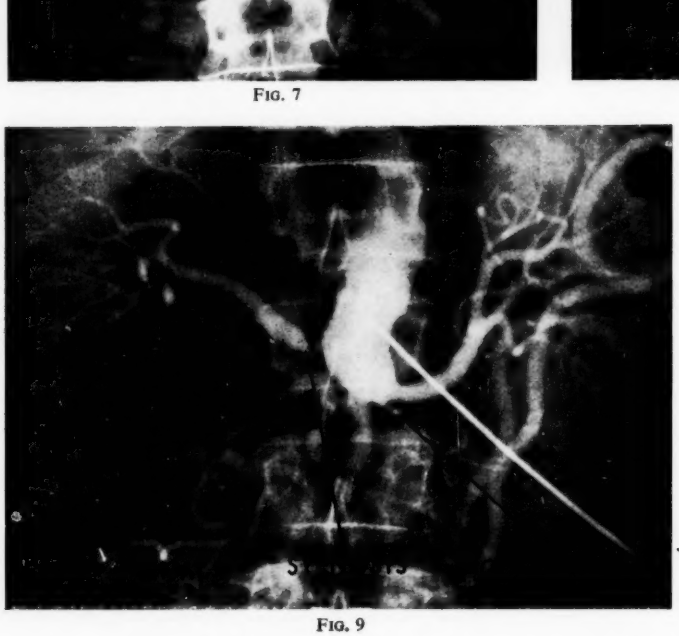
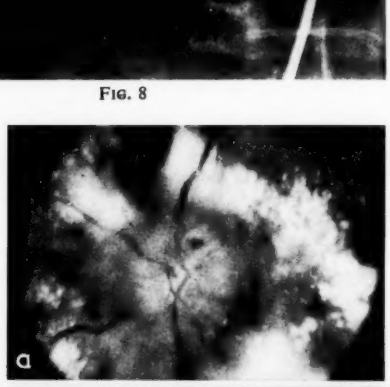
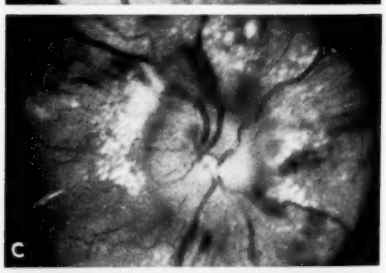


FIG. 9





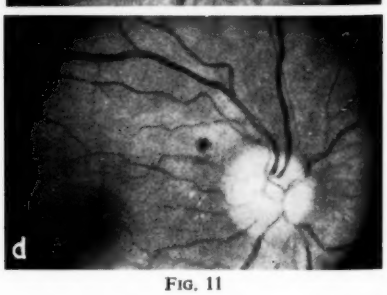


FIG. 11

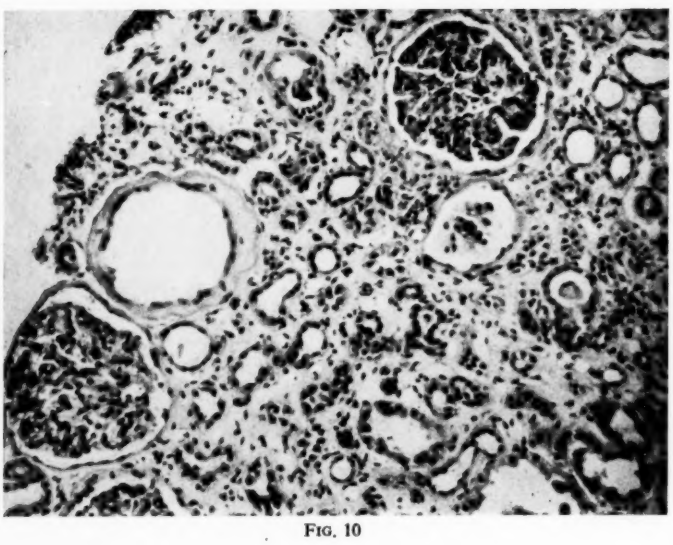


FIG. 10

exceptions. Even when the affected kidney is distinctly small (Case 18), better contrast may be obtained on that side.

Renal Arteriography

This procedure is of great value in the diagnosis of renal artery stenosis. Three different techniques are available. The first is simple translumbar aortography, the second is aortography by percutaneous transfemoral catheterization using the method of Seldinger (1953), and the third is percutaneous selective renal arteriography using an opaque catheter (Ödman, 1956). Any of these will provide good visualization of the renal arteries. Some workers are strong protagonists of one method as against the others, but all have merits and demerits, and the exact technique used is largely a matter of personal preference. We have used all three procedures during the last seven years. The majority of our patients have, however, been investigated by selective renal arteriography, mainly because this gives the best visualization of the peripheral renal vessels and of the kidney itself, and will, as shown in the illustrations (Figs. 2, 6, and 8, Special Plate), demonstrate renal-artery stenosis very adequately. The two other techniques are less difficult and will usually show a stenosis equally well (Fig. 9, Special Plate, Case 15).

Selective Renal Arteriography: Method

The procedure adopted is a personal modification by one of us (D.S.) of the technique described by Ödman (1956). An opaque catheter, premoulded with an appropriate curve at its tip, is inserted percutaneously from the femoral artery and passed into the mouth of the renal artery under screen control. Ödman uses a different catheter for each side; this involves withdrawing one catheter after use and replacing it by another. We have simplified the procedure by shaping a catheter in such a way that it can be inserted into either renal artery, and both sides can thus be injected with a single catheter. It has been found helpful to have side holes near the catheter tip so that the lumen of the aorta and the proximal part of the renal artery are also shown on the film. One of the alleged difficulties of selective renal arteriography is the presence of double renal arteries. This has not been found to present any particular difficulty in our cases, and we have frequently catheterized both arteries in these instances. A free injection of dye into the aortic lumen may, if necessary, be made before withdrawing. With the selective method excellent renal arteriograms are regularly achieved, using small doses of diatrizoate (5 ml. of "hypaque" 45% or "urografin" 60%).

We have encountered one patient (Case 14) in whom a diagnosis of renal artery stenosis was suggested wrongly by selective renal arteriography (Fig. 4, Special Plate). In this man the catheter tip virtually occluded the lumen of the artery supplying a small, irregular, and probably pyelonephritic kidney. The film taken at injection also demonstrated an apparent renal-artery stricture. Organic stenosis was not confirmed by ureteric catheterization studies (Table IX), by pressure measurements at operation, or by subsequent examination of the artery after nephrectomy, and it was presumed that the appearance was due to a jet effect as the contrast left the catheter tip. In several other cases where a small artery was virtually occluded, however, no such appearance was produced.

It must be stressed that all these angiographic techniques have their hazards, particularly in the presence of hypertension, with or without impaired renal function. None of them is to be undertaken lightly or by the inexperienced.

Operative Findings and Treatment

Presence of a Bruit in the Affected Renal Artery.—This almost constant finding was mentioned earlier.

Direct Measurement of the Renal-artery Pressure

It is essential to measure, by direct arterial puncture at operation, the pressure in the renal artery distal to the stenosis. Normally, the pressure in the main renal artery is almost identical with the pressure in the adjacent aorta, and, unless a distinct pressure-drop across the site of the supposed obstruction is found, the diagnosis of a truly functional renal-artery stenosis should be strongly queried, whatever the arteriographic appearances suggest. We have seen four patients (Cases 5, 12, 14, and 17) in whom renal artery stenosis was diagnosed on arteriography (Figs. 3 and 4, Special Plate), but in whom there was no pressure-drop or alteration in the pulse wave distal to the site of the supposed narrowing. In two of these (Cases 5 and 14), ureteric catheterization studies had been performed and, as we have described above, had given results which were not typical of renal-artery stenosis.

Case 17 provided several problems. In this patient a left-renal-artery stenosis was suggested by a denser pyelogram on the left, and free aortography demonstrated a stricture near the origin of the left renal artery. Ureteric catheterization studies showed, during the course of the test, urinary sodium and chloride concentrations, which in some periods were higher on the suspect side than on the right. The inulin and P.A.H. concentrations, however, were persistently higher on the left. At operation the renal-artery narrowing was confirmed, though no pressure-drop was found across the stricture. Biopsy of the left kidney showed atrophy of proximal convoluted tubules and sclerosis of a majority of glomeruli, but few vascular changes—appearances typically found distal to a renal artery stenosis. It is possible that in this patient structural damage in the kidney consequent upon main renal-artery obstruction was occluding the renal vascular bed and secondarily maintaining a high pressure in the renal artery distal to the stenosis. DeCamp and Birchall

LEGENDS TO SPECIAL PLATE

FIG. 7.—Intravenous pyelogram with water-loading in Case 3 20 minutes after the injection of the dye. No contrast is seen on the normal side, though the side with the renal-artery stenosis is clearly demonstrated.

FIG. 8.—Selective renal arteriogram in Case 1, showing stenosis at origin of right renal artery, with post-stenotic dilatation.

FIG. 9.—Aortogram in Case 15, showing lower aortic occlusion and right-renal-artery stenosis.

FIG. 10.—Biopsy from upper pole of Case 2 (first operation), showing tubular atrophy.

FIG. 11.—Case 2. (*a*) Photograph of left fundus before nephrectomy. Papilloedema, haemorrhages, and gross exudate. B.P. 260/160. (*b*) Photograph of left fundus five months after left nephrectomy. Fundus almost clear. B.P. 150/90. (*c*) Right fundus before nephrectomy. (*d*) Right fundus after nephrectomy.

(1958) have recommended that if there is no pressure-drop across the site of the presumed stricture, renal-artery surgery should not be performed. We are not fully convinced that such a finding necessarily excludes significant renal-artery stenosis. Patients of the type discussed above merit further study.

It is, of course, essential to check the pressure in the artery distal to the site of the previous obstruction at the completion of a reconstructive operation. The procedure cannot be regarded as successful unless the pressure in the renal artery has been restored to the level of the adjacent aortic pressure. Figs. B and C show the pressure tracing obtained at operation in Case 3. Before reconstruction, no pressure was recordable in the main renal artery distal to the stenosis. This is probably the result of the lowering of the systemic arterial pressure by anaesthesia to well under the levels normally prevailing (the aortic pressure is around 115/80 in the record; pre-operatively the blood-pressure was of the order of 230/140). Distortion of the renal pedicle by traction might readily collapse the distal renal artery in these circumstances. After thromboendarterectomy and spleno-renal anastomosis, the pressures in the aorta and main renal artery were practically identical (Fig. C). This phenomenon of unrecordable pressure in the renal artery at operation was seen also in Case 1. The point is of some importance, since under operative conditions

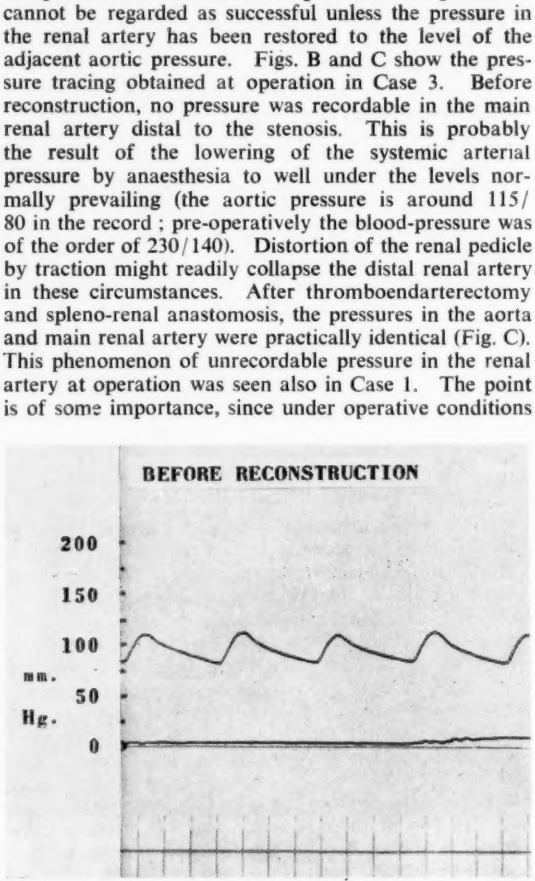


FIG. B.—Case 3. Pressure tracings obtained at operation, before reconstruction. Upper tracing, aortic pressure; lower tracing, left-renal-artery pressure.

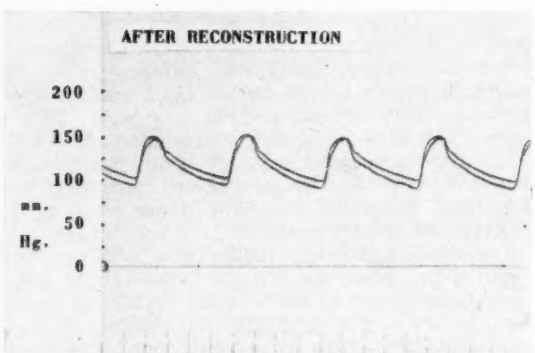


FIG. C.—Case 3. Pressure tracings obtained at operation, after reconstruction. Simultaneous aortic and left-renal-artery pressures.

the kidney distal to a renal-artery stenosis may be acutely ischaemic for a good deal longer than is represented by the time during which the renal artery is actually clamped. Acute tubular damage may, of course, occur in the operated kidney and persist for several days (Peart, 1959). Undue lowering of the blood-pressure during the operation should therefore be avoided. Further measures designed to protect the kidney, such as whole-body hypothermia or local renal cooling (Birkeland *et al.*, 1959), will probably be more widely employed in future.

Surgical Procedures

Surgical procedures have been described by Poutasse (1956), DeCamp and Birchall (1958), Owen (1959, 1960), and Yendt *et al.* (1960).

In most patients a reconstructive operation is desirable, since the kidney distal to the stenosis is potentially the better of the two, being protected from hypertensive damage by the stenosis. We are still uncertain of the extent of damage which is reversible, and it is important to preserve functioning renal tissue so far as is possible. The basis of conservative procedures is to restore adequate arterial pressure and blood-flow to the kidney with the minimum of acute interference with its blood supply at operation. Interruption of the blood-flow to the opposite kidney is avoided so far as is possible.

Thromboendarterectomy.—The removal of an atheromatous plaque from the renal artery, together with any thickened intima at the origin of the vessel, is a relatively quick procedure, though it may occasionally be difficult to gain access to the origin of the artery on the right side because of the close relationship of the vena cava and renal vein.

Spleno-renal Anastomosis.—The splenic artery is of comparable size to the renal and is usually long enough to be anastomosed to the distal renal artery on the left. It is not always necessary to remove the spleen in this operation, since it may be nourished by the short gastric arteries.

Renal Artery Reimplantation.—The renal artery may be divided and anastomosed to a new site in the aorta. Alternatively, side-to-side anastomosis of the renal artery to the aorta may be performed below the level of the stenosis.

Excision of Stricture.—The usual site of an atheromatous plaque is at the mouth of the renal artery. Occasionally, however, renal-artery stenosis occurs as a result of fibromuscular proliferation of the media, the origin of the artery being spared. In this event the stricture may be excised and end-to-end anastomosis performed.

By-pass Grafting.—A by-pass graft may be inserted from the aorta to the distal renal artery.

Nephrectomy.—This operation is indicated in cases of complete occlusion of the renal artery. Nephrectomy may also be the operation of choice in patients in poor general condition, provided adequate function has been demonstrated in the opposite kidney.

Results of Surgical Treatment

There were no operative deaths in the series. Nephrectomy or reconstructive surgery was performed in six cases (Nos. 1, 2, 3, 4, 11, and 19) in which a diagnosis of renal-artery stenosis was established beyond reasonable doubt. The hypertension was of a severe order in

all six cases, and in three (Nos. 1, 2, and 19) the optic fundi showed bilateral papilloedema, exudates, and haemorrhages. Exudates and haemorrhages, but without papilloedema, were present in Cases 3 and 11. Surgical treatment was followed in all of these patients except one (Case 4) by a fall in the blood-pressure to normal levels, with resolution of the retinal abnormalities (see Fig. 11, Special Plate, and Robertson, 1960). Cardiac size was reduced and there was disappearance of electrocardiographic signs of left ventricular strain. In no instance was there clinical or electrocardiographic evidence of myocardial infarction which might be held responsible for the fall in blood-pressure. This last point is important, since renal-artery stenosis occurs in a group of patients particularly prone to ischaemic heart disease.

Three earlier cases (Nos. 6, 10, and 20) were operated upon after less adequate investigation, the diagnosis of renal-artery stenosis responsible for the hypertension consequently being less surely established. In only one of these three (Case 20) was surgery successful in lowering the blood-pressure.

One further patient (Case 17) had a normal blood-pressure at the time of writing, but this case was operated upon too recently for proper assessment.

Medical Treatment

For various reasons, seven cases of the series have been treated with hypotensive drugs. Cases 8 and 13 were not operated upon, since no lesion was demonstrated radiologically. In Case 9 reconstructive surgery was not possible, and medical treatment was here regarded as preferable to nephrectomy. In Cases 4, 6, and 10 surgical treatment was not followed by a fall in blood-pressure, and these cases have since been controlled medically. In Case 2 thromboendarterectomy was unsuccessful, thrombosis of the renal artery occurring a few days after operation. Subsequent medical treatment was ineffective, and the blood-pressure remained high until nephrectomy was performed.

Though less satisfactory than successful surgical therapy, hypotensive drugs can be useful in the treatment of hypertension due to renal artery stenosis.

Renal Histology

Renal biopsy has been performed routinely at operation, specimens being taken in each case from kidney tissue distal to a stenosis and, wherever possible, either from the opposite kidney or from an unaffected segment of the same kidney. For convenience the biopsies have been taken from the subcapsular region; examination of the whole kidney in those cases where nephrectomy has been performed suggests that the subcapsular zone is the part likely to be most affected by an ischaemic process. The specimens are not, therefore, necessarily representative of the overall renal histology.

Kidney Distal to the Stenosis

Vascular changes have rarely been seen distal to a renal-artery stenosis, suggesting that the lesion protects the vessels from the effects of the raised blood-pressure.

The most constant and most striking change has been tubular damage, though the severity of this has varied widely from case to case. The proximal convoluted tubules have been most severely affected and showed some change in almost every instance. Moderately severe changes are shown in Fig. 10 (Special Plate), this biopsy being taken from the upper pole of the kidney of Case 2.

The glomeruli have seemed less sensitive to ischaemia, and showed little or no histological abnormality in the cases where tubular damage was slight. In the more severely affected cases, however, various lesions have been found in and around the glomeruli, such as thickening of the capillary basement membrane (Cases 1 and 2), fibrosis of Bowman's capsule (Cases 4 and 9), and more or less widespread glomerular sclerosis (Cases 6, 9, 11, and 17).

In the most severely affected areas of the ischaemic kidney, interstitial fibrosis and lymphocytic infiltration have been found.

In Case 19, with complete occlusion of the renal artery, coarse scarring and fibrosis were present, with numerous infarcts and a few remaining areas of normal tissue.

The histology in the three cases in which no pressure-drop was found across the site of an apparent stenosis is of particular interest. Cases 12 and 17 showed tubular atrophy and glomerular sclerosis, appearances which could well result from ischaemia. Case 5 showed extensive tubular atrophy and some sclerotic glomeruli, but also hyalinization of arterioles and thickening of small arteries. The position here was complicated by the presence of a hydronephrosis.

It is interesting that we have not encountered fibrinoid renal arteriolar necrosis in any proved cases of renal artery stenosis on either side, even where gross hypertensive retinopathy has been present, though in Case 10 fibrinoid necroses were found in the kidney distal to the supposed lesion. In this woman the diagnosis rested solely upon the arteriographic appearances, and we would now regard the case as quite inadequately investigated. The ureteric catheterization studies were unsatisfactory, and renal-artery pressures were not measured at operation. Reconstruction of the renal artery was performed, but the blood-pressure remained high, and has since been controlled with hypotensive drugs. The significance of the renal histology is therefore uncertain.

Opposite Kidney

In contrast to the ischaemic kidney, vascular changes have been prominent on this side. Arteries of all sizes have shown intimal thickening and fibrosis, with elastic hyperplasia and medial hypertrophy. Hyalinization of small arteries and arterioles has been seen frequently. As in the ischaemic kidney, glomerular sclerosis, interstitial fibrosis, and round-cell infiltration have been common. However, the tubules have usually been healthy in appearance on this side, though occasional small areas of tubular atrophy have been found.

The renal histology seen in these cases is in general agreement with the findings in experimental hypertension produced in animals by clamping the renal artery. The closest similarity appears to be with the changes occurring in the kidneys of the rat, this animal most closely resembling man in that severe and persistent hypertension may follow the placing of a clip on one renal artery, the other kidney and renal artery remaining untouched (Wilson and Byrom, 1939). The dog and the rabbit differ from man and the rat in that persistent hypertension is produced usually only if both renal arteries are clamped, or if one renal artery is clamped

and the opposite kidney removed. For the dog, similar changes to those found in man and the rat distal to the renal artery stenosis have been described by Goldblatt *et al.* (1934) and by Child (1938). In the rabbit, in experiments where clips have been applied to both renal arteries, one kidney has usually been found to show extensive tubular atrophy with or without glomerular changes, while the other kidney has shown little or no histological abnormality. Where the rabbit has had one kidney removed and a clip applied to the opposite renal artery, little histological change has been found in the remaining kidney even when severe hypertension has developed (Wilson and Pickering, 1938). There is general agreement for all species that vascular lesions are uncommon distal to a renal-artery clamp.

Discussion

Earlier reports (Poutasse, 1956; Birchall *et al.*, 1958) suggested that the investigation of possible renal-artery lesions might be restricted to certain well-defined groups of patients. Subsequently it has become apparent that renal-artery stenosis is by no means restricted to these groups, and our present experience indicates that renal-artery stenosis should be considered in any patient whose hypertension is otherwise unexplained. As we have pointed out, however, certain historical features may be strongly suggestive of a renal-artery lesion.

There is no short cut to the selection of patients who will be improved by surgery, and, since many aspects of this condition remain obscure, full investigation on the lines indicated here is advisable before an operation is carried out.

No case should be subjected to surgery unless there are definite indications for this. Many of these patients have widespread arterial disease and are unfit to withstand a prolonged operation. Nephrectomy is occasionally advisable, but more often the affected kidney is potentially the better one, and must be preserved if at all possible. A reconstructive operation requires the services of an experienced vascular surgeon, together with measures designed to minimize acute ischaemic changes in the kidney at operation. We are firmly of the opinion that facilities for the measurement of renal-artery pressures at operation are essential to the success of reconstructive procedures.

Renal-artery stenosis as a cause of severe hypertension provides a condition where appropriate surgery may be most rewarding, and there is little doubt that many of these cases have previously passed unrecognized.

The mechanism of the raised blood-pressure in this syndrome remains to be elucidated.

Summary

The presenting symptoms are not necessarily helpful in the diagnosis of renal-artery stenosis.

A systolic bruit over the affected artery is frequently present.

Critical evaluation of the intravenous pyelogram may be of great help. On the side with the stenosis there will often be seen better contrast, but with evidence of reduced urine-flow. The affected kidney may also be smaller than its fellow. In a minority of cases an impaired pyelogram is found on the side with the lesion.

No single investigation permits the diagnosis of renal artery stenosis as a cause of hypertension. Ureteric catheterization studies and renal arteriography are the most valuable investigations, and must be regarded as complementary rather than rival.

Direct arterial pressure measurement should always be made at operation, and a satisfactory reconstructive result checked by further measurement at the completion of the procedure.

We thank the various physicians and surgeons who have referred cases to us, and particularly Professor C. G. Rob. We are also grateful to Drs. N. Coghill, J. C. L. Adams, and M. J. D. Newman for permission to quote from the early records of Case 19. For the histological interpretations we are indebted to Dr. R. H. Heptinstall. Technical assistance has been given by Messrs. F. Diggins, A. Taylor, P. Harris, and D. Pullen, Misses G. Stean, D. Ross, R. Statham, and M. Tooley, and Mrs. N. N. Mendelson. Dr. Peter Hansell kindly provided the fundus photographs.

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The Government is to review the *Antioxidant in Food Regulations, 1958, and the Antioxidant in Food (Scotland) Regulations, 1958,* considering in particular the kinds of antioxidants to be permitted, the foods in which they may be used, the maximum allowance for permitted antioxidants, and labelling requirements. Representations on these points should be addressed to the Assistant Secretary, Food Standards Division, Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, London, S.W.1, or to the Secretary, Department of Health for Scotland, St. Andrew's House, Edinburgh, 1, and should arrive by December 31. Details may also be obtained from these two addresses.

USE OF SPIRONOLACTONE AND HYDROCHLOROTHIAZIDE IN TREATMENT OF OEDEMA

BY

R. O. FARRELLY, M.B., Ch.B., M.Sc.
Research Fellow, N.Z. Medical Research Council

R. N. HOWIE, M.B., Ch.B.
Medical Registrar

AND

J. D. K. NORTH, D.Phil., M.B., Ch.B., M.R.C.P. M.R.A.C.P.
Physician

Medical Unit and Central Laboratory, Auckland Hospital, Auckland, New Zealand

Over the last few years it has become increasingly apparent that excessive aldosterone secretion plays some part in the genesis and maintenance of oedema, whether this be due to congestive cardiac failure, the nephrotic syndrome, or hepatic cirrhosis (Luetscher and Johnson, 1954; Axelrad *et al.*, 1955; Duncan *et al.*, 1956; Dyrenfurth *et al.*, 1957). Considerable interest therefore is attached to the diuretic action of the 17-spirolactone steroids developed by Kagawa *et al.* (1957). Most investigators are agreed that these compounds act as specific aldosterone antagonists (Wolff *et al.*, 1957; Liddle, 1957, 1958; Salassa *et al.*, 1958; Ross and Bethune, 1959).

Two early spirolactone derivatives, SC.5233 and SC.8109, showed promise in the treatment of oedematous patients (Liddle, 1957, 1958; Bolté *et al.*, 1958) and of cases of hepatic cirrhosis with ascites (Kerr *et al.*, 1958). The former compound, however, was not active by mouth; the second was, but only in large doses. A new derivative, spironolactone (SC.9420), which is more potent, has recently been developed (Gantt and Dyniewicz, 1959), and the purpose of this study was to investigate its clinical value.

Aldosterone secretion is low in normal subjects on a high-sodium intake, and in oedematous patients who have achieved a "steady state" and therefore are not actively retaining sodium. It is not surprising that spironolactone has little diuretic effect on normal people (Liddle, 1957). This study of the effect of spironolactone was therefore carried out under conditions in which aldosterone secretion would be expected to be greatly increased—namely, in patients with active sodium retention, on a low-sodium diet and normal potassium intake.

The diminishing response to diuretics which occurs within a few days is of clinical importance, because a new steady state may be achieved in which the patient still has oedema. This effect may well be mediated by aldosterone, and it is the response of such "resistant" patients to aldosterone antagonists that is the subject of this investigation.

Methods

There are manifest difficulties in assessing the relative merits of two diuretic regimes. Not the least are the spontaneous diuresis which may occur when a patient is first rested in bed and the fact that the initial diuresis is usually better than that obtained by later therapy. The diuretic effects in this study were compared in units of four days; this time was chosen because it was felt that in any shorter period random variations might obscure the picture, and that if longer periods were used patients might lose their oedema before the trial had finished.

The seven patients were therefore admitted to a metabolic unit, kept at bed rest on a diet constant with respect to sodium (22 mEq/day), potassium (78 or 65 mEq/day), and fluid (1,600 ml./day). The investigation of each patient was divided into four periods, each of four days.

First period (days 1–4), diet and bed rest.

Second period (days 5–8), diet, and hydrochlorothiazide 200 mg. daily in equal six-hourly doses.

Third period (days 9–12), diet, hydrochlorothiazide 200 mg. daily, and spironolactone 800 mg. daily in equal six-hourly doses.

Fourth period (days 13–16), as for period 2.

In two of the seven cases period 2 was lengthened to 5–9 days to ensure that apparent trends were continued if spironolactone was withheld.

A daily record was kept of weight, blood-pressure, volume of urine, and degree of oedema. Biochemical investigations included daily urinary output of sodium and potassium (flame photometer), chloride (Van Slyke and Hiller, 1947), ammonia (Conway, 1950), and titratable acidity (Henderson and Palmer, 1914). Blood was taken by venepuncture thrice weekly for estimation of serum concentration of sodium and potassium (flame photometer), chloride (Van Slyke and Hiller, 1947), carbon-dioxide content (Van Slyke and Cullen, 1917), creatinine (Bonsnes and Taussky, 1945), and urea by a method using urease and Nessler's reagent.

At least once for each subject during the trial, a duplicate day's diet was prepared and analysed for sodium and potassium (by wet-ashing an aliquot of the homogenized diet, the final estimation being done on a flame photometer). At the end of the study, a creatinine-clearance test and a specific gravity concentration test were performed on each subject.

Results

Congestive Heart Failure

Clinical Aspects.—Details of the five patients (Cases 1–5) are set out in Table I. In three, ischaemic heart disease without recent myocardial infarction was responsible for the congestive heart failure, and chronic valvular disease in the other two. Oedema had been present for 1 to 36 months, but was gross in only two patients. Each had received routine diuretic therapy outside this unit before the trial was started. In all but one case every trace of oedema disappeared under the combined regime of hydrochlorothiazide, spironolactone, and a low-sodium intake. Blood-pressures fell during the 16-day trial in most patients, but in general the changes were not clinically significant. No patient had hypertension, and the blood-pressure seemed more dependent on the state of hydration than on the diuretic being used. Four of the five patients responded well to the treatment described, weight losses of between 3.2 and 12 kg. being obtained over the trial period. Case 5 did not respond.

Loss of Weight.—Fig. 1 shows that hydrochlorothiazide, which was the first drug given, was responsible for the greater part of the fall in weight in most

patients. The addition of spironolactone did not significantly affect the rate of fall, except in Case 4 (see Figs. 1 and 3).

Urine Excretion.—A summary of the results of the urine analysis is shown in Fig. 2, in which the average daily excretions of sodium, potassium, chloride, total acidity (ammonia plus titratable acidity), and urinary volume are plotted. Hydrochlorothiazide caused a significant increase in urine volume, sodium, potassium, and chloride, which was diminishing rapidly by the fourth day. When spironolactone was added there was little increase in urine volume, but in most patients the sodium excretion rose, and in all patients the potassium excretion fell markedly to levels below daily intake. When spironolactone was withdrawn, sodium excretion fell and potassium excretion rose slowly to the high levels obtaining at the end of period 2. All patients were in a state of negative potassium balance while receiving hydrochlorothiazide, but in positive balance when spironolactone was added. Total acid excretion showed no significant changes, except in period 3, when there was a minor reduction.

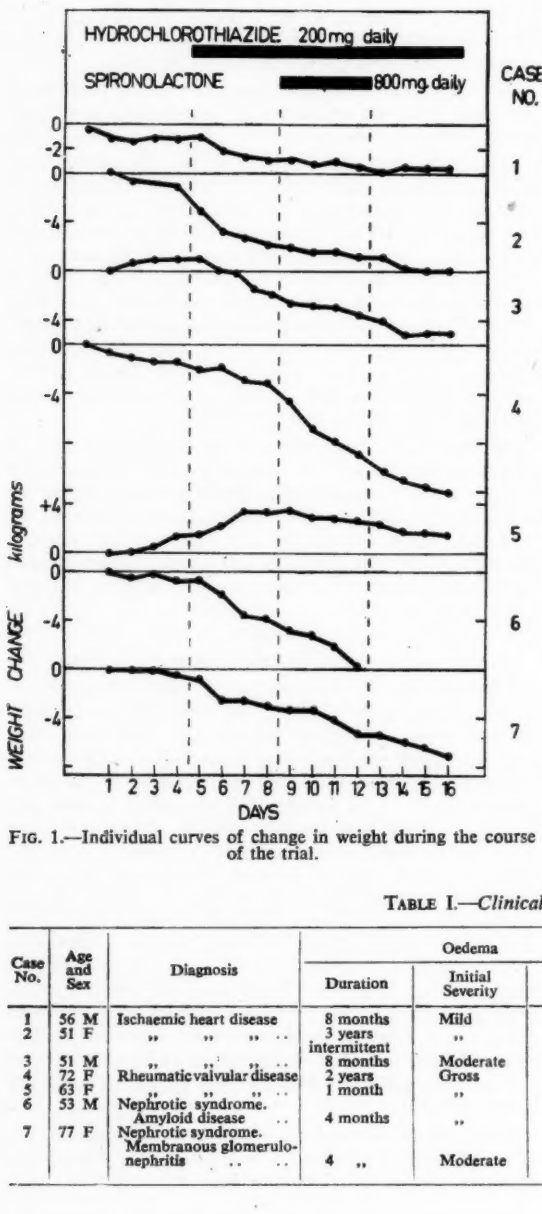

FIG. 1.—Individual curves of change in weight during the course of the trial.

Serum Levels.—The changes in urinary excretion were accurately reflected in serum concentrations: thus serum sodium levels slowly fell over the period of the trial, some patients becoming very hyponatraemic; this presumably was a result of marked sodium excretion without an accompanying increase in urine volume. Serum potassium levels also fell considerably when hydrochlorothiazide alone was being given (the lowest level was 2.6 mEq/l.) but rose again during the period of combined therapy. As might be expected from the urinary excretion of titratable acidity the carbon-dioxide content of the serum did not change significantly during the trial in any patient.

Nephrotic Syndrome

Clinical Aspects.—The cause of the nephrotic syndrome was, in Case 7, combined membranous and proliferative glomerulonephritis; in this patient renal function was greatly impaired, the blood urea remaining between 50 and 70 mg./100 ml. In Case 6 renal amyloid disease was responsible for the nephrotic syndrome. The diagnoses were made by renal biopsy.

Loss of Weight.—In both cases there was a significant loss of weight; the rate of fall in weight was not altered by spironolactone administration.

Urinary Excretion.—In both cases hydrochlorothiazide administration was followed by an increase in urinary volume, sodium, and potassium. The addition of spironolactone to the regime caused, in one subject only, further increase in sodium excretion and a reduction in potassium; Case 7 responded minimally to spironolactone. In both, the proteinuria persisted unchanged.

Side-effects.—No side-effects were observed during treatment with spironolactone, except for one patient who complained of muscular cramps. This may not have been related to therapy.

Discussion

The dynamic equilibrium between intravascular and extravascular fluids is dependent on venous pressure, colloid osmotic pressure, capillary permeability, and tissue turgor. However, it has been apparent for many years that generalized oedema is difficult to explain on this basis alone, and that some other factor or factors are involved.

TABLE I.—*Clinical Details of Patients*

Case No.	Age and Sex	Diagnosis	Oedema			Treatment Month Prior to Trial			
			Duration	Initial Severity	Final Severity	Bed Rest	Low-salt Diet	Mersalyl	Chloro-thiazide
1	56 M	Ischaemic heart disease	8 months	Mild	Nil	Yes	Yes	Yes	Yes
2	51 F	,, ,, ,, ..	3 years intermittent	,,	,,	No	No	No	,,
3	51 M	,, ,, ,, ..	8 months	Moderate	,,	Yes	,,	Yes	No
4	72 F	Rheumatic valvular disease	2 years	Gross	,,	,,	,,	,,	Yes
5	63 F	,, ,, ,, ..	1 month	,,	Gross	,,	Yes	,,	No
6	53 M	Nephrotic syndrome. Amyloid disease ..	4 months	,,	Nil	,,	,,	No	,,
7	77 F	Nephrotic syndrome. Membranous glomerulo-nephritis	4 ,,	Moderate	Mild	,,	No	,,	,,

TABLE II.—*Detailed Biochemical Results*

	Case No.	Period 1 Days				Period 2 Days				Period 3 Days				Period 4 Days			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
SODIUM mEq/day	1	14	25	34	32	161	107	51	22	61	64	75	69	36	23	21	17
	2	42	40	28	71*	208	106	90	24	47	49	51	33	30	10	8	8
	3	8	10	19	16	104	79	55	30	75	90	94	108	46	56	7	25
	4	34	41	18	—	—	—	62	26	226	181	146	144	105	44	49	15
	5	2·4	4·4	4·4	10·5	29	35	8·5	45	58	59	65	39	70	9	34	11
	6	33	24	37	31	186	198	91	89	73	110	159	†	†	†	†	†
	7	20	26	31	33	124	105	126	120	94	132	124	105	100	94	60	42
	Mean	22	24	24	32	135	105	69	51	91	98	102	83	65	39	30	20
POTASSIUM mEq/day	1	45	35	34	41	108	97	103	113	73	53	46	33	49	73	88	130
	2	35	31	47	48*	122	117	98	88	79	48	41	38	41	53	58	66
	3	30	28	70	72	63	63	52	46	22	15	26	58	66	75	53	57
	4	30	33	56	—	—	—	47	67	26	29	29	29	45	35	41	34
	5	6·8	12	10	32	37	35	13	46	42	25	38	21	52	8	62	11
	6	32	32	34	32	50	59	56	60	46	36	37	†	†	†	†	†
	7	47	58	53	53	71	90	55	63	33	45	46	51	47	64	69	69
	Mean	32	32	43	46	75	76	71	69	46	36	38	38	50	51	62	61
VOLUME ml./day	1	1,300	1,560	1,490	1,710	2,520	2,180	1,640	1,480	1,690	1,570	1,750	1,630	1,390	1,770	1,970	1,720
	2	1,810	1,920	1,520	1,960*	2,640	2,080	2,000	1,870	1,630	1,540	1,650	1,310	1,420	1,280	1,380	1,250
	3	820	910	1,670	1,560	1,900	1,580	1,640	1,310	1,560	1,100	1,700	1,830	1,350	1,450	900	1,130
	4	1,230	1,000	1,000	—	—	—	1,380	1,420	2,430	2,070	1,900	1,750	1,640	1,000	1,230	810
	5	260	390	280	670	620	470	170	860	710	540	640	420	890	135	1,230	160
	6	650	670	970	610	1,840	2,340	1,260	1,350	1,020	1,110	1,830	†	†	†	†	†
	7	1,300	1,470	1,600	1,720	2,150	1,750	1,920	2,000	1,570	2,100	1,880	1,960	1,810	1,840	1,550	1,500
	Mean	1,050	1,130	1,220	1,370	1,940	1,730	1,430	1,470	1,520	1,430	1,620	1,480	1,420	1,250	1,380	1,100

Collections were unsatisfactory in Case 4, days 4–6, owing to nocturnal incontinence. * Patient received 50 mg. hydrochlorothiazide 6 hours before end of collection period. † Patient withdrawn from trial owing to acute abdominal condition.

More recently it has been shown that the urine of patients accumulating oedema contained abnormally large amounts of a "sodium retaining factor" (Deming and Luetscher, 1950; Singer and Wener, 1953). Following the characterization of aldosterone, this steroid was soon shown to be identical with the sodium-retaining factor (Luetscher, *et al.*, 1954, 1956). The evidence that aldosterone plays a significant part in the development and maintenance of oedema is now impressive and is reviewed elsewhere (August *et al.*, 1958).

Of particular interest clinically are those patients who are "resistant" to conventional diuretics such as the mercurial drugs and the more recently developed benzothiadiazine drugs (chlorothiazide and related compounds). It seems a reasonable hypothesis that aldosterone secretion may be in part responsible for the gradually diminishing response to diuretics; eventually a state is reached where sodium excretion equals sodium intake. This steady state may occur when the patient is still oedematous; and if it is indeed fixed by competing effects of aldosterone and a diuretic, then the giving of spironolactone should alter the equilibrium in the direction of a diuresis.

It is also possible that aldosterone may be responsible for the fact that total exchangeable potassium in oedematous patients is low (Birkenfield *et al.*, 1958), and for the further potassium depletion which follows administration of chlorothiazide and related compounds (Bayliss *et al.*, 1958). Oedematous patients who had not responded well to conventional diuretic therapy were therefore investigated by the protocol set out above.

The results obtained in this study (Table II) confirm the potassium-losing properties of hydrochlorothiazide, and also that this undesirable effect can be effectively controlled by spironolactone. The potassium-retaining effects of spironolactone observed under the conditions of this trial are more dramatic than those found by other investigators using earlier aldosterone

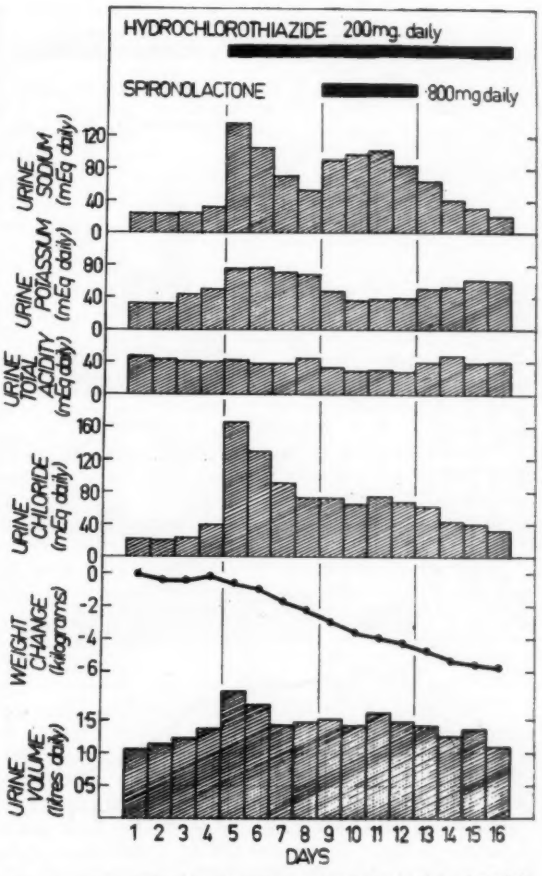

FIG. 2.—Mean values for all seven patients included in the trial. For detailed results see Table II.

antagonists under different experimental conditions. The diminishing sodium-losing response to hydrochlorothiazide shown by most patients is in this study a more rapid process than found by other observers, but this may be a result of the high dosage of hydrochlorothiazide. After four days on hydrochlorothiazide, most patients were approaching a plateau of steady excretion of sodium and potassium. On the addition of spironolactone to the regime there was an increase in the sodium excretion and a fall in potassium excretion (see Fig. 2).

By interpolation between period 2 and period 4, it is possible to arrive at a very approximate figure for the sodium loss and potassium retention caused by spironolactone. These derived data show that the ratio of sodium loss to potassium retained varied widely, and could not be correlated satisfactorily with any other clinical or biochemical parameters.

Also there is a great disparity between the effect of spironolactone on electrolyte excretion on one hand and water excretion on the other. If, as seems probable, spironolactone is a potent inhibitor of aldosterone, this would suggest that there is also a separate abnormality in water metabolism. This has been suggested by other workers, and the role of antidiuretic hormone in the aetiology of oedema has been discussed by Buchborn (1959). The experience of Kerr *et al.* (1958) and of

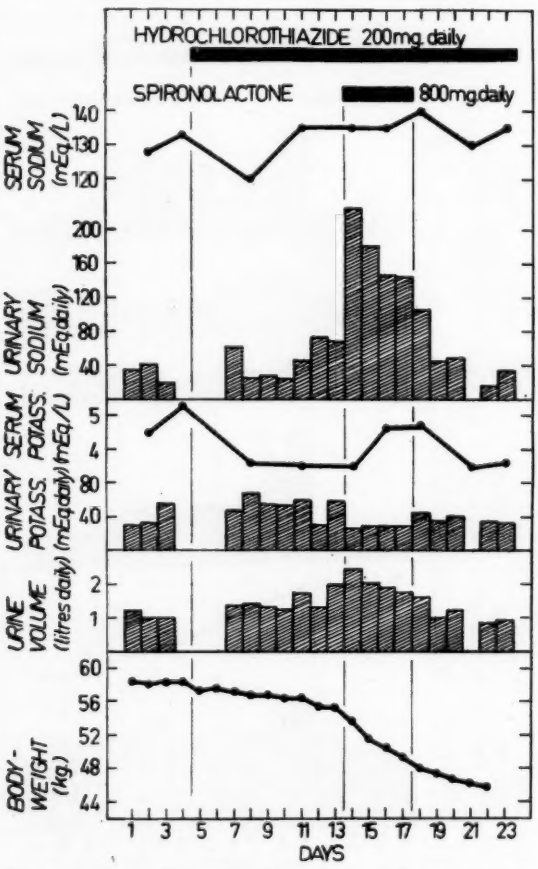

FIG. 3.—Case 4. The only patient with a marked increase in diuresis on combined therapy. Nocturnal incontinence prevented complete collections on four days.

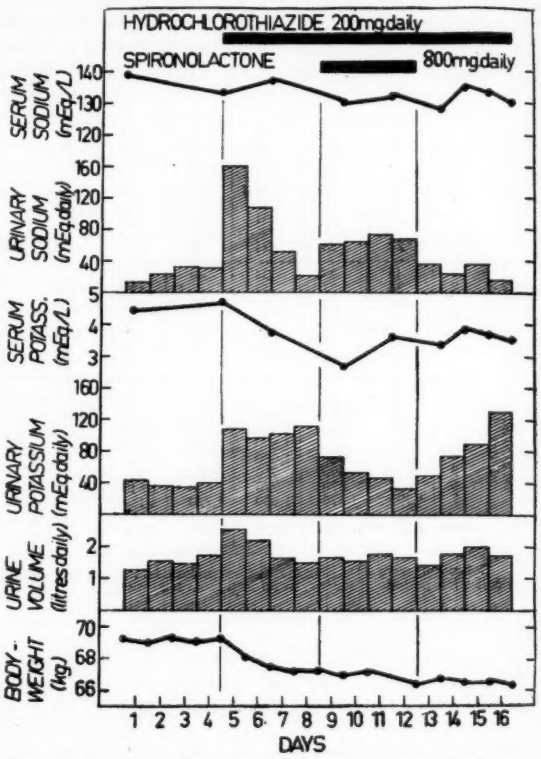

FIG. 4.—Case 1. To indicate the response in a typical patient.

Liddle (1958), that oedematous patients with renal insufficiency do not respond to aldosterone antagonists, parallels our own, and suggests that in such patients aldosterone is relatively unimportant. It is of interest to note that Case 7, who responded least well to spironolactone, was the only patient who did not exhibit a rapidly diminishing response to hydrochlorothiazide. Case 4 was the only patient (see Fig. 3) who showed a marked increase in diuresis during combined treatment. A more typical response is shown in Fig. 4 (Case 1).

Clinically, it appears that aldosterone antagonists are most effective in preventing potassium wastage during orthodox diuretic therapy. This can perhaps more easily be done by potassium chloride supplements, but some patients find this unpleasant, and some excrete so much potassium in the urine that supplementation is difficult. In this trial we have found clear evidence that spironolactone is of help in removing excess sodium from the body, but the effect on the removal of oedema fluid is less convincing.

Summary

A new steroidal spirolactone, spironolactone (SC.9420), was used in conjunction with hydrochlorothiazide in seven patients with oedema, five with congestive cardiac failure, two with the nephrotic syndrome.

In six of the seven patients the addition of spironolactone caused a significant increase in the sodium excretion and a marked reduction in the potassium excretion induced by hydrochlorothiazide in all patients.

These preliminary results suggest that spironolactone is of limited value in the treatment of cases of refractory

oedema, but that it will protect the patient against the known hazard of hypokalaemia associated with the use of hydrochlorothiazide.

We thank the New Zealand Medical Research Council for making it possible for one of us (R. O. F.) to participate in this trial. Spironolactone ("aldactone") was kindly supplied by Dr. C. Gantt, of G. D. Searle and Company, Chicago, and hydrochlorothiazide ("esidrex") by Dr. A. K. Pittman, of Ciba Laboratories Ltd., England. We are also indebted to Mr. D. A. Fisher for technical assistance.

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"At the North London [Miss Buss's school], in addition to regular drill and gymnastics, there were special remedial exercises for girls with crooked spines or other disabilities. An annual medical inspection by a woman doctor was started in 1882, possibly at the instigation of Elizabeth Garrett Anderson, who had become a Governor a few years earlier. . . . The first medical inspection at the North London revealed the alarming facts that only one girl in five measured had a straight spine and three out of eleven normal sight. To take a single example, a girl of 14 'has had rickets and now has attacks of momentary stupour, especially when at all pressed to work. Will gain much from the gymnasium, but must be treated . . . as a child of eleven or twelve.' . . . There was no medical inspection at Cheltenham [Ladies' College] in Miss Beale's lifetime. . . . If a girl showed signs of strain or illness a doctor was immediately called in; but Miss Beale felt that the responsibility belonged to parents and not teachers, and she did not favour the idea of a regular medical inspection." (*How Different from Us—Miss Buss and Miss Beale*, by Josephine Kamm, Bodley Head, 1958.)

MULTIPLE SCLEROSIS

A NOTE ON SOCIAL INCIDENCE

BY

HENRY MILLER, M.D., F.R.C.P.

ALAN RIDLEY, M.B., M.R.C.P.

AND

KURT SCHAPIRA, M.B.

From the Neurological Department, Royal Victoria Infirmary, Newcastle upon Tyne

It is an impression commonly held among neurologists that patients with multiple sclerosis tend to be above the average in attractiveness and intelligence, and that there is a relative preponderance of sufferers in the higher-income groups of the population.

One of us (H. M.) must admit to a long-standing suspicion that the condition was proportionately commoner in private than in hospital practice, and was surprised at the result of subjecting this impression to numerical analysis. Amongst 2,193 consecutive new out-patients referred to this department between 1956 and mid-1959 there were 198 cases of multiple sclerosis (9%); 2,203 approximately contemporaneous private consultations yielded only 116 cases (5%). The fallacies of interpreting these figures in terms of social-class prevalence are obvious, and they do little more than confirm the notorious unreliability of "clinical impression."

A survey of multiple sclerosis in Northumberland and Durham furnished material for a more direct assessment of the social incidence of the disease. All 519 general practices in Northumberland and Durham were approached for information about the total number of patients registered in each practice and the number of established cases of multiple sclerosis among them. Information was obtained from 352 practices, covering a total of approximately 1,400,000 patients of all ages; 700 cases were reported in which a diagnosis of multiple sclerosis had been made, almost invariably after consultant reference. Personal neurological examination of these patients reduced the number of authenticated cases to 662, which gives a prevalence rate of 47 per 100,000 of the total population at risk. However, figures drawn from a population of 466,714 under the care of practitioners personally known to us for the scrupulousness with which they keep their medical records and the readiness with which they refer patients for specialist opinion yield a prevalence rate of 59 per 100,000. Any such figure is certain to be an underestimate, if only because of the delay which ensues between the appearance of the initial symptoms and the making of a firm diagnosis; but we believe that the higher figure represents a closer approximation to the true prevalence, and that there are probably no fewer than 1,100 established cases in the whole region, which has a total population of 2,262,292 (1951 census).

The patients yielded by the survey comprised 390 females and 272 males, giving a sex-distribution of 58.9% female and 41.1% male—figures closely comparable with those reported from Northern Ireland by Allison and Millar (1954), whose 644 cases comprised 56.1% females and 43.9% males.

Analysis of Material

The 271 males with multiple sclerosis in this series provide the main material for the present study, since reliable information on social-class distribution of males in Northumberland and Durham over the age of 15 is available (1951 census). We have omitted one male patient in whom the disease began before the age of 15, since such an inclusion would have no comparative validity. The Registrar-General's categorization by social class is expressed in five groups—class I, professional, etc.; class II, intermediate occupations; class III, skilled occupations; class IV, partly skilled occupations; class V, unskilled occupations. The census analysis by occupation does not, however, include the 25,409 males in the two counties who were neither "occupied" nor "retired," and most of these were at school or attending other places of higher education. We have therefore added this number to the census figure, allocating them to the Registrar-General's social classes I, II, and III in the proportions in which these classes were represented in the remainder of the population at risk.

Social classification of the patients was based on their occupation at the time of the onset of the disease, and reliable information was obtained on this score from all the patients seen. In the Table the distribution of these 271 patients among the social classes I to V is shown together with that of the male population at risk, which we take to be aged 15 and over.

The probability of this finding being due to chance is less than one in a thousand. The main contribution to this highly differential social incidence consists in the large number of observed as compared with expected cases in class I, and the obverse finding in class V.

In the case of the 388 female patients (see Table) we have taken as the basis of classification the woman's own occupation at the date of onset of the disease if she was single and working at that time, her husband's occupation if she was married, and the father's occupation in cases of single women who were never employed—for example, because of the onset of the disease. Two females in whom the disease began below the age of 15 were not included in the analysis for reasons given above. No direct information is available about the social class distribution of the female population at risk.

In this instance the highly significant differential social incidence is due to the high ratio of observed to expected cases in classes I and II and to the obverse finding in classes IV and V. Again the probability of this finding being due to chance is less than one in a thousand.

The general correspondence between the male and female patients with multiple sclerosis in the matter of class distribution, except for a marked discrepancy in relation to class IV, is shown in the Table.

Percentage Distribution by Social Class of 271 *Male and* 388 *Female Patients with Multiple Sclerosis in Northumberland and Durham Compared with that of the Male Population at Risk and* 112 *Further Cases Drawn from Randomly Selected Practices of Doctors in Same Area whose Patients were Not Included in the Initial Survey*

Social Class:	I	II	III	IV	V
271 male patients with multiple sclerosis	5	14	56	19	6
388 female patients with multiple sclerosis	4	17	63	11	5
Male population of Northumberland and Durham over 15 years	2	10	53	21	13

Discussion

The figures, like most relating to multiple sclerosis, are suggestive rather than conclusive. The complete coverage of the material at our disposal would favour the validity of the class analysis, and the striking correspondence of the findings in male and female cases indicates the homogeneity of the group of patients with multiple sclerosis as a whole.

We are unimpressed by the suggestion that the relative preponderance of patients in the higher-income groups might be related to the relative hypersensitivity of such patients to neurological symptoms, and by its corollary that an appreciable number of people in classes IV and V may be the subjects of multiple sclerosis without themselves being aware of it. There is no evidence of such a differential threshold under current conditions of medical practice in the United Kingdom, nor that the wealthy seek medical attention more often than the poor.

There is, however, one outstanding weakness in our presentation so far. The 659 patients on which it is based represent a sample constituting about two-thirds of all the cases of multiple sclerosis in the population at risk, and not the total number of cases. We have studied the locations of the 167 general practices in Northumberland and Durham from whom we received no information, and we find no correlation with the differential geographical distribution of social classes within the area. Nevertheless it might be that these 167 practices covered a disproportionate number of patients in social classes IV and V and that the addition to our series of the cases of multiple sclerosis included in these practices might redress the social differential we have demonstrated.

It was thought essential to try to overcome this difficulty by analysis of a sample of patients drawn from this initially excluded population. For this purpose a financial inducement was offered to the principals of a randomly selected group of practices, self-excluded from the main survey, to notify their cases of multiple sclerosis.

Sixty-three general practitioners were approached, and it is of some interest that in 17 of these practices there were no recognized cases of multiple sclerosis: this had sometimes been the reason for the doctor's failure to reply to the original questionary. These 63 doctors and their partners were responsible for the medical care of 325,752 patients of all ages, and this group yielded 112 further cases in which a firm diagnosis of multiple sclerosis was established by re-examination—a prevalence rate of 34 per 100,000. Forty-three of these patients were male and 69 female (38 and 62% respectively). The percentage distribution in the five social classes of this random sample of patients was 6, 15, 59, 12, and 8 respectively and is remarkably similar to that of the other groups.

Confirmation of the above findings by similar analysis of case material drawn from other surveys—perhaps especially those which have aimed at the complete coverage of smaller populations—would furnish data demanding integration with any hypothesis dealing with the aetiology of multiple sclerosis. There are a number of "diseases of relative affluence." The higher incidence of paralytic poliomyelitis in the higher-income groups is usually attributed to the lower level of immunizing exposure to the causal virus under sheltered and sanitary living conditions, while there is considerable evidence

that the somewhat analogous social distribution of coronary thrombosis is related to the physical activity of occupation.

We are unaware of any comparable figures in the literature of multiple sclerosis, but the Registrar-General (1958) presents a social analysis of patients dying of this disease which is based on social status at the time of death. No correlation was found between multiple sclerosis and social class among men aged 20–64, but in married women of all ages and in men over 65 there was a steep mortality gradient with a relative predilection for the two highest classes. Our figures relating to social status at the onset of the disease reveal no such sex differentiation, and it has seemed to us that part of the discrepancy between the two groups of figures might be related to the social decline which is often the fate of the family when the husband is affected by the illness and may have to abandon his original occupation. If, on the other hand, it is the wife who develops multiple sclerosis there is no change in her husband's occupation and no consequent decline in her social status. A further factor may be concerned in the social gradient evident in both sexes over the age of 65; prolonged survival is almost certainly favoured by the extra care commonly associated with improved economic circumstances.

This investigation was carried out with the financial support of the North-East Multiple Sclerosis Trust and the Board of Governors of the Royal Victoria Infirmary, to both of which we are grateful. We also thank Professor J. N. Morris, of the Medical Research Council's Social Medicine Research Unit, for his helpful criticism and advice.

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TEACHING OF PSYCHIATRY AT NATIONAL TAIWAN UNIVERSITY

BY

TSUNG-YI LIN, M.D.
Professor of Psychiatry, National Taiwan University

The introduction of modern psychiatry to Taiwan—a society with traditional Chinese culture and social institutions on the one hand and the transitional uneasiness arising out of rapid industrialization and modernization on the other—called for special consideration and careful planning. Psychiatry had held almost no position in medicine and public health in the 50 years since the introduction of modern medicine; this was regretted, but was regarded as not entirely a disadvantage at the inception of a mental health programme, because there would be no need to revise or abolish obsolete or undesirable practices and regulations, or to retrain the personnel.

As a first step, census surveys of a sample population in three communities—rural, small town, and urban—were carried out from 1946 to 1948; they yielded a clear picture of the prevalence of mental disorder and its relationship to social factors (Lin, 1953). This became the basis of the mental health programme.

Given the lack of trained psychiatric personnel of any category, the magnitude of mental health problems revealed by the surveys constituted a special challenge when it came to formulating and implementing a long-term programme. To this end an intensification of the undergraduate teaching of psychiatry was designed and became the central focus of the activities of the Department of Neurology and Psychiatry of the National Taiwan University Medical College in the first ten years of its establishment.

The reasons for this decision were: (*a*) The training of specialized personnel alone never catches up with the needs of the community. Properly trained general physicians should be able to handle mild psychiatric problems. (*b*) Since the surveys revealed that over 95% of patients lived at home, one questions the wisdom of erecting gigantic mental hospitals as the major policy of the mental health programme. Home care and rehabilitation programmes should be the main emphasis, and therefore local practitioners should be trained in this respect. (*c*) The public health services which were originally developed for combating organic, especially communicable, diseases should be regarded as prospective resources for community mental health programmes. (*d*) For the sound development of psychiatry as a specialty in medicine, the attraction of young, intelligent, and properly motivated graduates is essential.

In summary, instead of concentrating on training specialists to meet the psychiatric problems, emphasis was to be laid upon the integration of psychiatry into the medical curriculum for training medical students in understanding and forwarding the mental health programme.

The character of the medical curriculum is difficult to change, particularly so when it has to do with psychiatry. It was due to a combination of the following circumstances that it was possible to remodel the teaching of psychiatry at the National Taiwan University Medical College. In 1953 and 1954 the medical curriculum of the university underwent drastic revision; to increase efficiency the "block system" of teaching was adopted, and teaching hours were redistributed in accordance with modern medical trends. The recommendations regarding psychiatry of the two advisers on medical education* came as a surprise, both to the non-psychiatric faculty and to the psychiatry department, because in the place of 64 hours of lectures on psychiatry for the whole medical curriculum 16 hours were to be given as a course in medical psychology and 14 hours for neuropsychiatric diagnostics in preclinical years; each student was to have clerkship training for nine full weeks—a total of 300 hours in clinical psychiatry—and, moreover, half of the students were to spend six to seven weeks as interns in the final year. This intensification of psychiatric teaching was naturally regarded by the other departments as an invasion, and certainly presented a formidable task to the understaffed Department of Neurology and Psychiatry.

The timely publication of the report of the Ithaca Conference (American Psychiatric Association, 1952) made this seemingly impossible teaching load both a challenge to take its share of responsibility in medical education and an opportunity to forward the advance of psychiatry.

*Dr. H. Brown, Dean of the School of Public Health, Columbia University, and Dr. W. C. Davison, Dean of Duke University Medical School, were I.C.A. medical education consultants in Taiwan in 1953 and 1954.

Aims and Principles of the Teaching Programme

Psychiatry was taught: (*a*) as a specialty of medicine in treating mentally sick people; (*b*) as the introduction of psychosomatic medicine and the psychology of the physically ill; (*c*) as a part of the basic philosophy of medical education in presenting the concepts of the whole man and of sound doctor–patient relationships; and (*d*) from the point of view of its part in community health programmes through its presentation of the individual as a member of a family, society, and culture.

It was aimed to develop in the student:

1. The ability to conduct a good medical interview and to make pertinent observations concerning biological, psychological, and social aspects of behaviour in patients.

2. The ability to assess correctly the condition of patients who are emotionally disturbed and who may be expressing their distress in physical, psychological, or social symptoms. This implies a reasonable understanding of the zones of healthy and sick behaviour in a society, and, more particularly, the ability to differentiate between normal, neurotic, psychopathic, psychotic, and intellectually defective behaviour.

3. The understanding of what the physician who is not a psychiatrist can do and should do: (*a*) in the management and treatment of emotionally healthy people who have become sick, (*b*) in the management and treatment of emotionally sick people who may or may not have physical symptoms, and (*c*) in the management of disturbed patients, particularly those who may come to the general physician.

4. The understanding of the roles of other health workers and ability to work with other members of the therapeutic team.

The encouragement of self-education and critical thinking on the part of the students was regarded as essential. The following methods were used in addition to lectures which were confined to the preclinical years: (*a*) Seminars in groups of 16 to 18 students. (*b*) Case-work with out-patients as the main clinical teaching, with a view to presenting common psychiatric problems to the students. (*c*) Case conferences for instruction in intensive case-study. (*d*) Tutorial system—both for case-work and for seminars. (*e*) Research—students were encouraged to participate in on-going research projects.

The department consists of one professor, four lecturers (including one neurologist), one senior psychiatrist, one child psychiatrist, six residents, one consultant in psychiatric social work, and two psychologists. Either the professor or one of the lecturers takes charge of each group of clerk students for the entire nine weeks, assisted by the others as tutors. The class of 70 students was divided into four groups.

Outline of the Programme

Course in Medical Psychology.—The aim of this course is to prepare the student to acquire a broader concept of human biology and an understanding of the growth and development of human personality as a bio-psycho-social being. The following topics are discussed in the course: the meaning, scope, and applications of medical psychology and psychiatry; the conscious and the unconscious; the functions of the cerebral cortex; the function of the autonomic nervous system; the physiology of the hypothalamus in relation to emotion; the development of the child in relation to its environment; the concept of adaptation mechanisms; the structure and types of personality; social aspects of personality development; personality growth in relation to the Chinese family and culture.

Course on Neuro-psychiatric Diagnostics.—The aims of this course are to prepare the student for a better understanding of the psychology of the ill and of the importance of the doctor–patient relationship in a general medical setting, and to enable the student to observe and record the signs of subtle and gross abnormal behaviour.

Teaching Programme for Clerkship Students

This teaching is carried out at the Department of Neurology and Psychiatry of the Taiwan University Hospital and the attached Taipei Children's Mental Health Centre. The characteristic features of this clerkship-training programme consist, in the first place, of the students' active participation in clinical work with ambulatory patients. Two students form a team to deal with an unselected case every morning, one acting as the doctor and the other as a social worker. They complete the history of the patient, assess the nature and severity of the problem, and formulate plans for treatment. This is followed by the interview and examination of the patient by an instructor, who is a senior psychiatrist, who will discuss the case and comment on the case-work done by the students. This arrangement in the mornings enables each student to do case-studies under supervision on about 30 psychiatric patients, 15 neurological patients, and five children in the whole period.

The students are also present at the daily case conferences, which are attended by the staff of the Department of Neurology and Psychiatry and occasionally of other departments, doctors, nurses, social workers, psychologists, and occupational therapists. Two psychiatric cases, one a psychosomatic case and/or neurological case, and one child case are presented each week. These case conferences acquaint the student with the multi-disciplinary approach of the psychiatric team.

The daily student seminars provide the academic instruction, not only to impart knowledge of psychiatry and its relation to other medical disciplines, but also to help students to independent and critical thinking. In three weeks of nine seminar sessions the major topics in the textbook of psychiatry are covered. The next six weeks, 18 seminar sessions in all, are used for discussion of individual papers presented by each student. The topics are chosen from a prepared list which includes about 60 subjects, classified into six areas:

The Biological Basis of Mind.—This includes cortical function; cortico-subcortical relationship and consciousness; the physiological basis of emotion; electroencephalography.

Personality Development and Child Psychiatry.—The concept of mature personality; enuresis; hypochondriasis; effects of parental deprivation on mental health; effects of parental overprotection on mental health; juvenile delinquency; psychological testing.

Clinical Psychiatry and Psychiatric Treatment.—Heredity of psychoses; physiology of mental disorder; shock-therapy; psychotherapy; group therapy; occupational therapy.

Psychiatry and Medicine; Psychosomatic Medicine.—Theory; the concept of psychosocial medicine; headache; backache; peptic ulcer; hypertension.

Mental Hospital.—Psychiatric hospital as a centre for preventive work in mental health; an integrated mental health service; the advance from custodial to therapeutic patient care in mental hospitals.

Mental Health; Psychiatry, Community, and Law.—Epidemiology of mental disorder; interrelations between the

social environment and psychiatric disorders; cultural influences in personality development; the effect of urbanization on mental health; psychiatry and law.

For the presentation each student is assigned one instructor to help him to prepare the paper by reading articles and books, and, if necessary, carrying out some laboratory or practical experiment. Each presentation is followed by discussion among the students and with the instructors, with a final summing-up by the senior instructor. Through these seminars the student should obtain a general picture of the current problems and trends of psychiatry, and also the position and role of psychiatry in relation to medicine, public health, and society.

The students spend one week on a ward to acquaint themselves with the life of the patients, the therapeutic atmosphere, and the actual team-work in the therapeutic situation. Personal experience of the improvement in a patient's behaviour will usually correct some of the student's misconceptions about psychiatry and change his attitude to mental illness.

Neurology is taught with psychiatry as an integral part of the curriculum; seven seminars, nine case conferences, and two weeks of work in the outpatient department are allocated to it. This is designed to help the student to understand the integrative function of the central nervous system in relation to outside stresses and also to the internal organs.

For seven weeks before graduation one-half of the students take up psychiatry as part of their rotating internship training. The limit placed on the number of students is due to the restricted facilities available. The aims of the intern training are to develop the students' understanding and skill in psychological medicine, in order that they may deal with mild psychiatric problems with greater confidence. Three types of instruction are given. First, psychotherapy of two patients under supervision; secondly, actual experience in dealing with psychiatric problems in the emergency clinic; and, thirdly, further experience in a ward with treatment procedures both in physical and in occupational and rehabilitational treatment.

For graduation the student is required to present a thesis on one subject in the medical curriculum. Work on the thesis usually starts towards the second half of the clinical years. Since the implementation of this new teaching programme about one-fifth of the students choose a subject in psychiatry. These research activities have certainly been regarded as a most fruitful experience both by the students and by the staff.

Evaluation and Discussion

The results of the teaching programme remain to be seen and should be carefully weighed. No one can assume that the effects of a teaching programme run parallel with the thoughts and efforts put into it. The following observations, however, may justify my view that this programme should continue in Taiwan.

The morale of the staff of the Department of Neurology and Psychiatry has risen substantially since the inception of the new programme. Their enthusiasm in carrying out the programme has been remarkable; all the senior staff spend at least 18 hours a week with the students in clinical or seminar sessions and the person in charge of each block of clerkship teaching up to 24 hours. Their keen interest has also been reflected in the constructive comments on the students' responses, which have helped to improve the programme.

The response of students to the programme has been most encouraging. At the beginning of the clerkship programme the prevailing air, on the part of the student, of anxiety and prejudice against the scientific grounding of the psychological sciences gradually gave way to that of interest, active participation, and animated teacher–student relationship; however, usually one to three students in each group of 16 to 18 remained indifferent or even hostile. A measure of the genuine interest in psychiatry is given by the voluntary participation in the research projects and the large number of graduation theses written on this subject.

Another important feature is the appreciation expressed by students for the teaching method, which is strongly biased towards self-education. At the final session of each clerkship training period, when free discussion takes place, it has been a common experience for one or two students to volunteer statements, such as the following, with which many others agree: "I have learned, among other things, to think independently." "I resented at the beginning of the course the fact that we were not being taught as in the other departments; instead of being given the knowledge and theories in one, two, three order, we had to work hard in order to discuss the subjects intelligently in the seminars, but now I am glad that we have been taught in this way." "I feel more confident now of being able to organize and express my thoughts quickly."

The increase of more intelligent consultations on psychiatric problems from other departments may be the result of the intensive psychiatric instruction. The effects on the other departments, however, need more time for careful assessment. The ill-feeling among the staff of other departments caused by the increase of psychiatric instruction is still present, and may unfortunately continue until an objective evaluation of the contribution of psychiatry to medical education can be made and accepted.

There is still room for further improvement in this teaching programme. First, the teaching of medical psychology and psychiatric diagnostics in the preclinical years is not satisfactory for the instruction of the broader concept of human biology. Secondly, the need for more co-ordinated teaching with other clinical disciplines and public health is keenly felt. Thirdly, both students and staff recognize the desirability of following up patients and participating in the domiciliary services. Finally, some clinical experience in a mental hospital is desirable. This has to wait until an adequate therapeutic atmosphere prevails and competent psychiatric personnel are available for teaching in the hospital.

This teaching programme may, and will, change in accordance with the scientific evolution and the needs and resources of the time. The clear recognition of its dual responsibility—in taking a proper share in medical education and in preparing the ground for the growth of psychiatry and the mental health programme in Taiwan—should guide the future development of the programme.

Summary

The teaching programme in psychiatry at the National Taiwan University was devised to meet local needs and local conditions; surveys yielded a clear picture of the prevalence of mental disorders in the community, in

which the great majority of patients were cared for at home. Given the lack of trained personnel, it was felt expedient not to concentrate upon training an inevitably small number of specialists, but to guide the future physicians in understanding and forwarding the mental health programme and to instruct them to treat mild psychiatric problems competently.

To this end the teaching of psychiatry in the Medical School was intensified; a total of 330 hours, of which 300 consist of clinical clerkship training both in out- and in-patient departments, with direct contact with patients, case-conferences, seminars, etc., was devoted to it for all students, with, moreover, half the students spending six to seven weeks as interns in the final year. Psychiatry was taught: (*a*) as a specialty of medicine in treating mentally sick persons; (*b*) as an introduction to psychosomatic medicine and the psychology of the physically ill; (*c*) as a part of the basic philosophy of medical education in presenting the concepts of man as a bio-psycho-social unit and of sound doctor–patient relationships; and (*d*) from the point of view of its part in community health programmes.

Possible criteria for evaluating the success of this teaching programme are discussed.

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PRETIBIAL MYXOEDEMA

BY

T. M. D. GIMLETTE, M.D., M.R.C.P.

Senior Medical Registrar, St. Thomas's Hospital, London

Pretibial myxoedema is a condition in which there is local thickening of the skin by a mucin-like deposit; it is nearly always associated with exophthalmos and with past or present hyperthyroidism. Pretibial myxoedema is not rare, but most papers and textbooks dealing with the subject do not convey this, probably because only extreme examples are usually recognized. In a recent comprehensive review Graciansky, Leclercq, and Youénou (1957) collected 151 case reports, many of which were of single severe cases; some descriptions were purely dermatological, and exophthalmos and the endocrine state were unrecorded.

Present Investigation

Between April, 1956, and September, 1958, 280 patients with thyrotoxicosis were admitted to the medical wards of St. Thomas's Hospital; 12 of these (Table, Cases 1–12) had pretibial myxoedema or developed it later, an incidence of 4.3%. Transient lesions may well have been overlooked, and the true incidence was probably over 5%. Some findings in 23 patients (4 men, 19 women) with pretibial myxoedema are described, the lesions having been observed for more than a year in every case. The condition produced severe swelling of the feet and legs, causing some disablement in four patients; these four and two others also had thyroid acropachy (Gimlette, 1960) (see Table). The changes

FIG. 1.—Case 21. Early lesion (actual size 4 cm. across) showing thickening of skin and coarse hair, and involvement of minute scar at upper left edge of lesion.

in the other patients were milder and in some cases rather insignificant. The age at onset of pretibial myxoedema ranged from 31 to 64 years.

The earliest stage of pretibial myxoedema was a shiny red plaque a few millimetres in diameter, usually on the anterolateral side of the lower half of the leg. Several separate lesions often appeared simultaneously, sometimes first on one leg, sometimes quite symmetrically; they might progress no further, or regress, or the plaques might enlarge and grow together. The condition was seen unilaterally only in the early stage. The area of the lesion was usually quite bright red, particularly when warm, or it might appear cyanotic; when bloodless the lesions were yellowish. Often notably coarse hair grows, and excessive sweating occurs, in the area of the lesions (Fig. 1).

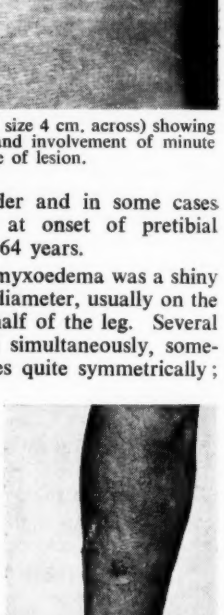

FIG. 2.—Case 4. Two years after onset of pretibial myxoedema. Changes in skin of foot resembling elephantiasis; earlier there had been pitting oedema. Biopsy scar on outer side of leg.

About half the patients complained of irritation, and the lesions occasionally became modified by lichenification and scaling. In the four most severe cases the lesion spread to involve most of the skin of the legs up to the knees; the ankles and feet were also involved, and in these latter parts there was hyperkeratosis; deep folds appeared in the thickened skin, and the appearance of the feet resembled that of elephantiasis (Fig. 2). In one such patient (Case 4) lymphangiography (Professor J. B. Kinmonth) showed normal lymphatics at the early stage, when there was pitting oedema of the feet; this later changed to hard

woody oedema. Lymphangiography has not been repeated since. There seems to be no particular tendency to infection despite the fissures and hyperidrosis in the affected skin. In one patient pretibial myxoedema developed on the dorsum of the foot after the original lesion had been excised and Thiersch-grafted, and also on the donor area on the thigh (Figs. 3 and 4); at the latter site particularly it had regressed after five years. The formation of tissue resembling keloid in appearance, where an area of pretibial myxoedema has been excised for biopsy (Fig. 2) or other reason, or after trauma, is very characteristic and is a contraindication to surgical intervention. There was also a definite tendency for developing pretibial myxoedema to be accentuated at the site of old scars. In Case 15 a small area of pretibial myxoedema appeared over the sternum. Localized lesions occurring above the knee, which are rare, are to be distinguished from lichen myxoedematosus or tuberous myxoedema.

It was thought unnecessary and undesirable to do a biopsy in most cases. The histological appearance in pretibial myxoedema is that of oedema of the corium, which contains a substance, staining like mucin, separating the collagen fibres. Chemical analysis has shown the mucopolysaccharide content to be increased greatly in the affected skin and to a less extent in the patient's unaffected skin elsewhere (Beierwaltes and Bollet, 1959), and hyaluronidase is certainly capable of softening this tissue. Possibly some of the orbital changes in severe exophthalmos are the same. The hyalase test (Kellgren, Ball, and Tutton, 1952) in the normal forearm skin of two patients with severe pretibial myxoedema was negative.

Of the 23 patients with pretibial myxoedema, all except one presented with hyperthyroidism; the exception (Case 15) was never hyperthyroid and presented with exophthalmos. In all the hyperthyroid patients except one exophthalmos developed at the same time as hyperthyroidism, or soon after, and before the hyperthyroidism was treated. Pretibial myxoedema was noticed at the time of onset of the other symptoms or soon after, and before any treatment, in 10 out of 21 patients.

In 22 hyperthyroid patients thyroidectomy was done, or some other form of treatment given, generally within a year of the onset of symptoms. The hyperthyroidism was apparently permanently controlled by the initial treatment in 14 patients; six were considered to have become hypothyroid after initial treatment and were thereafter given thyroid extract. Two of these patients developed severe exophthalmos, five developed severe or moderately severe pretibial myxoedema, and four eventually developed acropachy. On the other hand, in eight there was unsatisfactory control or relapse needing different or repeated treatment; these patients showed rather less tendency to severe progressive exophthalmos and pretibial myxoedema than the others (see Table overleaf).

Pretibial myxoedema was already present before hyperthyroidism was treated in nine patients: it increased in none, remained the same in five (two moderately severe), and decreased in four (one moderately severe). Pretibial myxoedema developed after treatment of hyperthyroidism in 13 patients; in four of them it became severe, and in three moderately severe. In these latter seven patients there was nothing, in retrospect, to show that severe pretibial myxoedema could have been anticipated. Severe pretibial myxoedema was associated with the later development of thyroid acropachy in six patients.

The above findings are summarized in the Table.

Treatment

Many different treatments for pretibial myxoedema have been advocated; the results are confusing, and it is clear only that there is no satisfactory answer. Mild lesions in hyperthyroid patients tend to resolve or to get

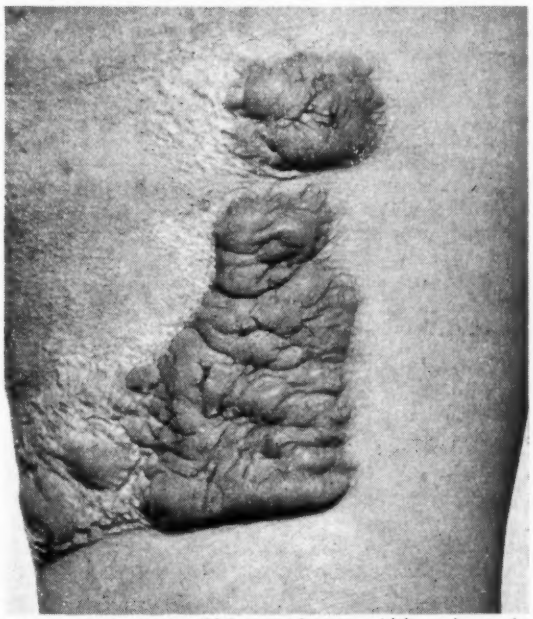

FIG. 3.—Case 14. Pretibial myxoedema on thigh at donor site two years after skin graft.

FIG. 4.—Same lesion as in Fig. 3, four years later. Regression has taken place, probably not attributable to treatment; changes of thyroid acropachy had recently developed.

no worse when the hyperthyroidism is cured, and no treatment seems to be indicated. The prognosis in severe pretibial myxoedema appears to be unaffected by treatment. In two patients with severe lesions, these had receded a little after 12 and 7 years after their onset (Cases 14 and 19). In any case, the treatment of hyperthyroidism or severe exophthalmos must take priority.

Treatment was attempted in some patients with progressing pretibial myxoedema. Thyroid given orally failed to produce any convincing change. Injections of triiodothyronine into the affected skin produced no local change, though doses of 200 and 400 μg. caused easily detectable general metabolic effects. Treatment with large doses of prednisone orally produced transient softening and recession of the lesions, but after two or three weeks on continued high dosage they returned to the previous state. Local injection of hydrocortisone was followed after two or three weeks by resolution, usually permanent, of some small lesions. This treatment left an area of slightly wrinkled skin, which was not noted after slower spontaneous resolution in other patients, in whom the lesions left no trace. Parts of larger lesions were affected in the same way by intensive local injection with hydrocortisone, but after about six months the treated areas tended to relapse. Local hydrocortisone injections produced little or no objective change in the elephantiasis-like areas around the ankle and on the toes. Local injection of hyalase (1,500 units in 1 ml.) produced a transient area of softening lasting up to two weeks in the lesions; attempts to infuse larger quantities in more dilute solution by subcutaneous drip were painful and ineffective. The combination of hyalase with hydrocortisone seemed to have no advantage.

Surgical excision and grafting were followed by recurrence in the grafted area and the donor site within a few months (Fig. 3) (Patterson, 1958). Local radiotherapy to the lesions had no effect, nor did radiotherapy to the pituitary. The generalized leg-swelling of extensive pretibial myxoedema was reduced very little by prolonged firm bandaging of the feet and legs, with massage of the skin and galvanism to the calf muscles.

Details of Cases

Case No.	Age and Sex	Hyperthyroid	Treatment of Hyperthyroidism	Exophthalmos		Pretibial Myxoedema		Time of Onset Before or After 1st Treatment of Hyperthyroidism	Acropachy
				Before	After	Before	After		
				Treatment of Hyperthyroidism		Treatment of Hyperthyroidism			
1	42 F	+	^{131}I*	+++	++	++	+	6/12 before	−
2	51 F	+	Carbimazole. ^{131}I*	++	+	−	+	3/12 after	−
3	56 F	+	^{131}I	++	++	+	−	3/12 before	−
4	47 F	+	Surgery†	++	+++	−	+++	1/12 after	+
5	40 F	+	^{131}I	+	++	++	++	3/12 before	−
6	57 F	+	^{131}I	++	++	+	−	3/12 ,,	−
7	43 F	+	^{131}I	+	+	−	+	4/12 after	−
8	45 F	+	Surgery. ^{131}I*	+	+	−	+	6/12 ,,	−
9	51 F	+	^{131}I	+	+	+	+	1/12 before	−
10	31 F	+	Surgery	+	+	+	−	8/12 ,,	−
11	45 F	+	Surgery	+	++	−	+	3/12 after	−
12	47 F	+	^{131}I†	+	+	−	++	4/12 ,,	+
13	35 F	+	Thiouracil. ^{131}I*	+	+	+	+	6/12 before	−
14	56 M	+	Surgery†	+	+++	−	+++	1 yr. after	+
15	42 M	−		+++		+			−
16	39 F	+	Surgery	+	++	−	+++	1/12 ,,	+
17	50 F	+	Surgery. ^{131}I*	+	+	−	++	1/12 ,,	+
18	50 F	+	Thiouracil*	+	+	+	+	8 yrs. before	−
19	36 M	+	Thiouracil†	+	++	−	+	1/12 after	−
20	50 F	+	Thiouracil. ^{131}I*	+	++	−	+	6 yrs. after	−
21	64 F	+	Surgery†	−	+	−	+++	8/12 ,,	+
22	63 M	+	^{131}I†	+	+	++	++	?/12 before	−
23	33 F	+	Surgery. ^{131}I*	++	++	−	++	3/12 after	+

* Relapse after treatment.
† Rendered hypothyroid.

\+ Mild exophthalmos.
++ Moderate exophthalmos with some external ophthalmoplegia.
+++ Severe exophthalmos with loss of vision or requiring decompression.

\+ Mild pretibial myxoedema.
++ Moderate pretibial myxoedema exceeding 100 sq. cm. in total area.
+++ Severe pretibial myxoedema resembling elephantiasis.

Discussion

The usual order of onset of symptoms is hyperthyroidism, exophthalmos, pretibial myxoedema, and in some patients acropachy. Mild pretibial myxoedema is not uncommon, either before or after treatment of hyperthyroidism, and it tends to resolve spontaneously. Severe pretibial myxoedema usually but not invariably occurs in patients with severe exophthalmos, and only in a minority of these. Sometimes thyroid acropachy develops later. In the present series severe pretibial myxoedema tended to occur in patients who did not have it at all before treatment of their hyperthyroidism, and in whom treatment induced hypothyroidism. The cause of pretibial myxoedema is obscure, and, while it is very doubtful that the lesion is caused by overtreatment of hyperthyroidism, its occurrence in a severe form in patients in whom hyperthyroidism was easily reversed may be significant.

The development of exophthalmos, pretibial myxoedema, and thyroid acropachy may be so far apart in time that it is not obvious that they have an identical cause. These conditions may each appear, progress up to a certain point, and then progress no further or even regress, while another in turn appears and progresses (Fig. 4). However, the almost invariable order in which the symptoms develop and the nearly constant association with hyperthyroidism has suggested a single stimulus responsible for all. This stimulus evidently can take a long time to produce its full effect, but all the tissue changes it produces may be essentially the same. The likeliest nature of the stimulus appears to be a hormone from the anterior pituitary; there have been various and conflicting views about this which cannot be considered in detail.

In pretibial myxoedema there is usually no evidence of dysfunction of the pituitary or of other endocrine glands apart from the thyroid. There have been reports of eosinophil adenoma (Freeman, 1958) and eosinophil hyperplasia (Levitt, 1954), each in a patient with pretibial myxoedema. In the present series there were no deaths and no radiological evidence of pituitary enlargement in the patients with severe pretibial myxoedema, nor was there evidence of any other endocrine disorder, and none of the patients was diabetic.

The theory that thyroid-stimulating hormone (T.S.H.) also caused exophthalmos has not been confirmed (Gilliland and Strudwick, 1956; Querido and Lameyer,

1956), and it has been suggested that there is a separate exophthalmos-producing substance (E.P.S.). The physiological role of this substance is puzzling and its assay is difficult. It has been claimed that E.P.S. can be separated chemically from T.S.H. (Dobyns and Steelman, 1953), that it can produce exophthalmos experimentally, and that excess of it in the serum of patients is correlated with exophthalmos (Dobyns and Wilson, 1954; Brunish, 1958). It has yet to be established that E.P.S. or any other substance is present in excess in the serum of patients who develop pretibial myxoedema and later acropachy. The concept that excess of a pituitary hormone produces change in certain parts of a target organ, the skin, is not yet proved and is unhelpful as a basis for therapy. At present one can only say that pretibial myxoedema in the skin is one of several localized disorders, perhaps essentially similar, which may appear in Graves's disease under certain circumstances as yet obscure.

Summary

In 23 patients with pretibial myxoedema the appearance and behaviour of the lesions, and their relationship with hyperthyroidism, are described.

Minor pretibial lesions are not uncommon; they usually soon resolve after hyperthyroidism has been controlled.

Severe pretibial myxoedema, when it develops, tends to do so after cure of hyperthyroidism and in association with severe exophthalmos. When the lesions become extensive they persist and are resistant to treatment.

I thank the physicians of St. Thomas's Hospital who have allowed me to describe patients under their care.

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"Roughly the same is true about the theory either of contraceptive measures or of treatment of sub-fertility. Although each of them contains some new elements each can be developed from the basic physiological and anatomical knowledge common to all doctors. The situation is utterly different with regard to the therapy of marital problems. First, our knowledge of the natural history of marriages is most rudimentary, it does not bear comparison with physiology and still less with anatomy. Since pathology and therapy of marriage is not part of the medical curriculum it follows then that the mere fact that someone has obtained a medical qualification does not mean that he or she will possess the skill required for this kind of work. Should a doctor want to treat marital problems he must be prepared, as in any other special branch of medicine, to learn a good deal, theoretically and practically." ("The Marital Problem Clinic," Dr. M. Balint, *Family Planning*, April, 1960.)

RETINITIS PIGMENTOSA, HYPERTENSION, AND URAEMIA IN WERNER'S SYNDROME

REPORT OF A CASE, WITH NECROPSY FINDINGS

BY

A. VALERO, M.B.

AND

B. GELLEI, M.D.

Clinical Lecturer of Pathology, Helrea University, Jerusalem

From the Medical Department "D" and the Pathology Department, Rambam Government Hospital, Haifa, Israel

In 1904 Werner described a peculiar disorder termed "cataract in connexion with scleroderma" occurring in four brothers and sisters. Oppenheimer and Kugel (1934) distinguished this condition from its related Rothmund (1868) syndrome and established the eponym "Werner's syndrome." In 1941 they reported the first post-mortem findings on such a case. In a comprehensive review of the condition Thannhauser (1945) emphasized that the skin changes were not true scleroderma. By 1953 Irwin and Ward listed 55 cases, and up to the time of writing the present article approximately 62 cases have been placed on record, with only one additional post-mortem description (Perloff and Phelps, 1958).

The manifestations of the fully developed syndrome may be summarized as follows: (1) Habitus: short stature, stocky trunk, and slender extremities. (2) Premature senility: appearance in the third or fourth decade of juvenile cataracts, grey hair, baldness, and arteriosclerosis. (3) Scleroderma-like changes: atrophy of skin and subcutaneous tissue, circumscribed hyperkeratosis, trophic ulcers about ankles and feet, and beaked nose. (4) Endocrine: tendency to diabetes mellitus, hypogonadism, thyroid-gland dysfunction, osteoporosis.

Only one manifestation may be prominent in the clinical picture, so that cases may be overlooked and regarded as juvenile cataracts, primary hypogonadism, scleroderma, or generalized arteriosclerosis. Our present case, the third with necropsy findings, is unusual as its presenting symptoms were uraemia and hypertension.

Case Report

A Persian Jew aged 39 was admitted to the Rambam Government Hospital on January 9, 1958, complaining of shortness of breath, persistent severe headaches, and frequent vomiting of five days' duration.

His past history revealed that as a child he was healthy. Between the ages of 18 and 19 he rapidly lost most of the hair on the top of his head without any apparent disease or illness. He had never married, as he was always poor and could not afford a wife, but he also admitted that he had never had a sexual urge or libido.

At the age of 30 his vision began to fail, gradually getting worse and worse until six years later he could only distinguish finger movements in front of his eyes. It was about this time, in December, 1954, that he was admitted to the eye department of the Rambam Government Hospital with bilateral posterior pole juvenile cataracts. After operation on the left eye his sight improved slightly, and on examination of the eyeground retinitis pigmentosa was

diagnosed. No disk changes were recorded on that examination or on others which followed. The blood-pressure fluctuated between 190 and 155 systolic and 120 and 100 diastolic. Blood urea was 20 mg./100 ml., and the urine was normal except for traces of albumin.

The family history revealed that his parents were first cousins. Two brothers died a few months after birth, of an unknown cause. His father died at the age of 73. His mother, two brothers, and two sisters were all alive and well. None was bald and none of them wore spectacles.

Examination showed him to be a small-statured, emaciated, bald, and bespectacled man, 160 cm. in height and weighing only 45 kg. He looked about 10 years older than his stated age, except for his body, which had a childish appearance with its relatively thin limbs and no hair on the chest, axillae, or pubis. His facial hair and moustache showed normal growth except for localized bald patches over the left cheek and upper lip. The top of his head was completely bald, and on the sides the hair was sparse and thin. There was baldness of the outer halves of the eyebrows, and the nose was beaked (Fig. 1). A number of teeth were missing; others were loose and about to fall. His voice was weak and hoarse.

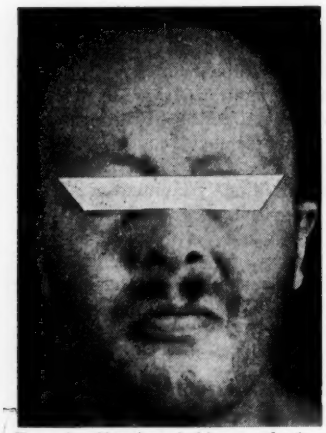

FIG. 1.—Showing baldness of the head and outer halves of the eyebrows.

He had a mature posterior cortical opacity of the right lens, obscuring detailed vision of the respective eyeground. The operated left eye revealed retinitis pigmentosa, but no other vascular or disk changes. He was almost blind in his right eye, and the vision in the left eye was limited to 4/50.

The skin was waxy pale, atrophic, and dry. Over the bony prominences of the ankles and feet it appeared glossy and tight, and could not be moved freely. One got the impression of there not being enough subcutaneous tissue between the skin and bones. On the thighs, gluteal regions, and lower back were circumscribed areas of dry, scaly, hyperpigmented skin. Other areas looked ichthyotic. The finger-nails showed fine longitudinal striations.

The chest was well developed, showing a slight asymmetric prominence over the praecordium to the left of the sternum. The lungs were slightly hyperresonant on percussion, but the breath sounds were normal. The heart was normal in size, with the apex beat in the fifth intercostal space within the mid-clavicular line. There was a soft grade I apical systolic murmur. A2 was accentuated. The pulse was regular 80/min., and blood-pressure 160–170/80–90. The abdomen was soft, flabby, and slightly protruding. The liver and the spleen were not enlarged on palpation. The thyroid gland was not enlarged and no nodules could be felt in it. The testicles were small like those of a child of 12 years. The penis was normal in size and appearance. Examination of the central nervous system revealed no abnormality.

Clinical Course and Laboratory Data

During the first week the patient continued to vomit and was in a state of severe dehydration and metabolic acidosis. Blood urea was 203 mg./100 ml., potassium 7.8 mEq/l., sodium 140 mEq/l., chlorides 100 mEq/l., calcium 9.7 mg./100 ml., phosphorus 6.7 mg./100 ml. The urine contained 1% albumin but no pathological sediment. Specific gravity measurements showed an isosthenuria with a maximum of 1006.

He was put on intravenous infusions to combat acidosis, and in an effort to shift the high serum potassium he was given 10 units of insulin half an hour before the main meals. At 11.40 p.m. of the second day after commencement of insulin he was found in a deep coma, covered with cold sweat. After 10 ml. of 50% glucose intravenously he rapidly regained full consciousness.

About two weeks after admission his condition improved, he ceased vomiting, and his blood electrolytes were restored to normal. Blood urea fluctuated between 120 and 160 mg./100 ml., urea clearance was 7.2%, and blood proteins were 6.1 g./100 ml., with 3.8 g. albumin. Cholesterol in blood was 246 mg./100 ml. Haemoglobin was 4.7 g./100 ml. R.B.C., 2,600,000; W.B.C. 12,000 (normal differential count). The haematocrit was 23%, M.C.V. 88 cubic μ, M.C.H. 30 $\mu\mu$g., M.C.H.C. 27%; thrombocytes 130,000. The bone-marrow was normal. The Khan serological test for syphilis was negative.

Retrograde pyelography and presacral insufflation gave the radiological impression of a small left kidney. Methylene blue injected intravenously was not excreted from either kidney after 20 minutes. Kidney biopsy was unsuccessful on two occasions and further increased our suspicion that the kidneys were small and inaccessible.

The following endocrinological examinations were carried out: 17-ketosteroids were found to be 14.8 mg. per 24 hours. No eosinophils could be found in the peripheral blood on repeated absolute counts. The F.S.H. was 24 u./l. The B.M.R. was −12% and the P.B.I. 3 μg./100 ml. The intravenous glucose-tolerance test showed a normal curve, but when performed by giving glucose orally a flat curve was obtained—namely, 95, 95, 108, 105, and 110 mg./100 ml. at half-hour intervals.

The electrocardiogram showed signs of strain on the left ventricle. An *x*-ray film of the skull revealed oxycephaly. *X*-ray films of the cervical spine showed no signs of osteoporosis. On fluoroscopy the left ventricle seemed slightly enlarged and the aorta wide for his age. No signs of arteriosclerosis were detected in the arteries of the legs.

The patient went slowly downhill. The blood urea remained high, reaching at times 220 mg./100 ml.; his blood-pressure gradually increased to 240/130; and finally he developed heart failure with pulmonary oedema. His vomiting returned and he lapsed into uraemic coma and died on March 12, 1958.

Post-mortem Findings

External examination accorded with the above clinical description.

Brain: Oedematous, with increase in amount of cerebrospinal fluid in the subarachnoid spaces. *Heart* (weight 370 g.): Both ventricles hypertrophic; aortic valves fenestrated, otherwise normal. Coronaries widely open. Approximately 100 ml. of clear fluid in pericardial sac. Severe fibrotic and atheromatous plaques in the aorta. Ostium of right renal artery occluded and does not permit entrance of probe (Fig. 2). *Respiratory system:* Trachea

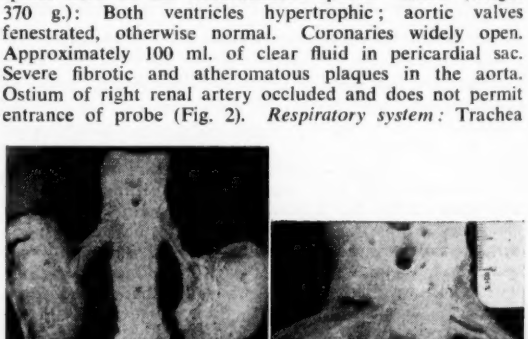

FIG. 2.—Showing the small contracted kidneys and detail of right renal artery obstruction.

and bronchi contain thick, purulent mucus; lungs emphysematous and oedematous. *Liver* (weight 1,500 g.): Dark brown in colour. Biliary system normal. Pancreas and gastro-intestinal tract—no abnormalities. *Kidneys:* Both very small (right 65 g., left 85 g.). Capsule strips easily. The external surface of left kidney is granular, of right fairly smooth. Small scattered cysts visible on external surface. On cut surface, parenchyma atrophied; no evident differentiation between cortex and medulla. *Bladder:* Mucous membrane inflamed. *Spleen* (weight 30 g.): Grossly normal. *Genital organs:* Prostate not enlarged; testicles very small (weight 5 g.). *Endocrine glands:* Hypophysis normal in shape and size. Thyroid smaller than normal; cherry-sized, white, hard nodule in left lobe; scattered white pea-sized nodules in right lobe. Adrenals of normal appearance. Parathyroids not enlarged.

Histological Examination

Nervous System.—No changes.

Respiratory System.—Small foci of bronchopneumonia.

Cardiovascular System.—Myocardium: few small perivascular cuffings by round cells. Aorta: intimal thickening and fibrosis. Right renal artery occluded by organized thrombus. In vessel wall, evidence of atheromatotic changes.

Digestive System.—Gastro-intestinal tract normal. Liver normal in structure; slight irregularity in shape and size of liver cells with many mitotic figures. Fine brownish pigment (lipofuscin) in several Kupffer cells. Pancreas: inspissated secretion in slightly dilated ductules.

Urinary System.—Glomeruli mostly obsolete and fibrotic. In remainder, slight thickening of capillary basement membrane, with fibrotic thickening of Bowman's capsule in some. Tubules generally atrophic, with areas of compensatory hypertrophy in patchy fashion. In atrophic tubules the basal membrane thickened and fibrotic. Several tubules showed cystic dilatation and contained hyaline casts and birefringent crystals (sodium urates; leucine?). Interstitial connective tissue increased and fibrotic. Diffuse round-cell infiltration, marked especially in the cortical zone and cortico-medullary junction. The interlobular and arcuate arteries revealed hypertrophy of the media and intima with splitting of the internal elastic membrane. The lumina narrowed. No manifest changes in the afferent arterioles. Bladder: haemorrhagic areas and acute inflammation of the mucous membrane.

Genital System.—Seminiferous tubules of various sizes, generally smaller than normal. Good spermatogenic activity in about two-thirds of tubules, but rather incomplete (no spermatozoa). The remaining tubules small and obliterated, partially or completely by loose connective and elastic tissue. The tubules widely separated by loose connective tissue. Groups of small Leydig cells visible in the vicinity of tubules. Prostate: Glandular lumina distended by large amyloid bodies. Several solid cords of transitional epithelium. Slight round-cell infiltration in stroma.

Endocrine Glands.—Hypophysis of normal size. Cell population normal. Pinhead-sized chromophobe adenoma in anterior lobe. Adrenals: small areas of nodular hyperplasia in fascicular zone; glomerular and reticular zones well preserved; scanty lipoids. Thyroid: irregularity in shape and size of vesicles; papillary adenocarcinoma in left lobe and small nodules of papillary adenocarcinoma in right lobe.

Spleen normal structure; small foci of haemopoiesis in sinusoids.

Skin from the extremities showed slight atrophy of the epidermis with moderate hyperkeratosis.

Discussion

The unusual appearance of the patient stimulated the search for a common cause of his cataracts, premature senility, and hypogonadism. Though hypertension and uraemia were not features of any of the reviewed cases of Werner's syndrome, their known predilection to generalized arteriosclerosis induced us to consider the attractive possibility that the hypertension and uraemia might be secondary to arteriosclerotic changes in the renal vessels. On post-mortem examination bilateral vascular contracted kidneys were found in spite of the fact that only the right renal artery was occluded. This points to a slow occlusive process—as enough time must have elapsed for collateral compensatory circulation to develop.

The functional and anatomical study of the endocrine system in this case and in the two previously reported post-mortem cases (Oppenheimer and Kugel, 1941; Perloff and Phelps, 1958) shows that no fundamental or characteristic glandular deficiency exists in Werner's syndrome.

None of these cases showed any structural abnormality of the pituitary gland, and the F.S.H. in our case was normal. The pin-head sized chromophobe adenoma is a common finding in post-mortem examinations and no significance can be attached to its presence.

Histologically the thyroid parenchyma was normal, except for the small nodules of papillary adenocarcinoma in the left lobe and the papillary adenocarcinoma in the right lobe. The protein-bound iodine of 3 μg./100 ml. is in the low range of normal and may be indicative of a mild hypothyroidism. This impression is further increased by the flat oral glucose-tolerance test and by the hypoglycaemic episode, which cannot be attributed only to the small dose of insulin which was given several hours beforehand.

The two consistently recurring endocrine abnormalities in Werner's syndrome are diabetes and hypogonadism. Only the latter existed in our case, and was manifested clinically by small testicles, impotence, and lack of libido. The normal masculinization with damage of part of the seminiferous tubules, normal Leydig cells, incomplete spermatogenic activity, and normal F.S.H. speak for a selective tubular injury of testicular origin. Tubular degeneration may be seen in chronic renal insufficiency, but in our case the sexual disturbances appeared long before his kidneys showed signs of failure. The patient stated that at no time did he ever experience sexual urge, whereas at the age of 36, when in hospital for the first time, his blood urea was still only 20 mg./100 ml.

The thyroid adenocarcinoma found in our case deserves comment, as it strengthens the impression that there is a relative increase in the incidence of neoplasia in these cases. Our case added to six other malignancies in 63 cases of Werner's syndrome (Agatston and Gartner, 1939; Oppenheimer and Kugel, 1941; Schott and Dann, 1949; Müller and Andersson, 1953; Ellison and Pugh, 1955), brings the incidence of malignancy to 11.1%.

The perivascular cuffing by round cells in the myocardium, the inspissated secretions in the pancreatic ducts and the anaemia are manifestations of uraemia. The increase in mitotic figures in the liver may be a manifestation of old age, though the presence of lipofuscin pigment in the Kupffer cells points to a post-necrotic regenerative process.

The retinitis pigmentosa, which occurred also in the case reported by Kleeberg (1949), is interesting and

deserves special comment. This disease is a primary degeneration of the neuro-epithelium of the retina on a hereditary basis, the importance of blood relationship among parents for the manifestation of the disease having been established (Nettleship, 1907–8).

Cataracts often complicate retinitis pigmentosa and are always present in cases of Werner's syndrome. If we accept the view that retinitis pigmentosa belongs to a group of hereditary diseases which have this in common, that the cells and tissues affected become prematurely senile (Verhoeff, 1931), then retinitis pigmentosa and the cataracts, common to the two diseases, are further evidence that Werner's syndrome is a heredo-degenerative disease of unknown origin. (It will be noted that our patient's parents were first cousins.)

From the foregoing it would appear that premature senile changes, rather than endocrinopathies, offer the best explanation for the functional and structural changes described in Werner's syndrome.

Summary

The clinical and post-mortem findings in a case of Werner's syndrome with uraemia and hypertension are described.

The renal failure was found to be due to vascular contracted kidneys and arteriosclerotic occlusion of the right renal artery.

The presence of retinitis pigmentosa in Werner's syndrome is an interesting finding which, together with other evidence, points to a heredo-degenerative disease in widely distributed body cells and tissues, affected by inherent characteristics which result in their degeneration.

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"Unlike Russian doctors, who are merely members of a branch of the Medical Workers Trade Union, Chinese doctors still retain their association. But though its journals continue to print some work of an international standard—which the *Chinese Medical Journal* presents in excellent English—the incessant political exhortations of some of the association's officers force one to conclude that they see themselves as primarily the representatives of government, not of the doctors who may elect them."—From a lecture by Dr. T. F. Fox, editor of the *Lancet*, at the 87th Annual Meeting of the American Public Health Association (*Amer. J. publ. Hlth*, 1960, **50**, suppl., 28).

TREATMENT OF CHRONIC FURUNCULOSIS

BY

L. G. TULLOCH, M.D.
Senior Dermatological Registrar

V. G. ALDER, B.Sc., F.I.M.L.T.
Bacteriologist

AND

W. A. GILLESPIE, M.A., M.D., F.R.C.P.I., D.P.H.
Clinical Pathologist
United Bristol Hospitals

Recurrent furunculosis is often caused by reinfection with staphylococci from the patient's carrier sites. Hobbs *et al.* (1947), Valentine and Hall-Smith (1952), and Tulloch (1954) have shown that the causative staphylococci often come from the patient's own nose. Gould and Cruikshank (1957) and Copeman (1958) have had considerable success in preventing recurrences of furunculosis by the use of antiseptic nasal creams.

Staphylococci from sites other than the nose may also cause furunculosis. Superficial lesions of the skin, such as eczema, otitis externa, and blepharitis, are sometimes colonized by staphylococci and may be important sources of reinfection. Areas of normal skin also are sometimes colonized by staphylococci, especially the perineum (Hare and Ridley, 1958; Ridley, 1959). We observed cases of recurrent furunculosis which were caused by staphylococci from the perineum.

We report here the results of treating chronic furunculosis by disinfecting the patients' anterior nares and other carrier sites and by eradicating staphylococcal carriage from members of their families.

Methods

The patients investigated were 58 adults who came to the dermatological out-patient department between January, 1957, and June, 1959, with histories of recurrent furunculosis of at least six months' duration. Several had suffered from boils and styes for years. Alternate patients were selected for the control and the test groups. 15 patients defaulted. After spending six months as controls, 13 patients were transferred to the test group. There were altogether 33 test cases and 23 controls, most of whom were followed up for at least six months from the beginning of treatment. A few were observed for only four months. Freedom from furuncles during this period was regarded as a cure.

At the first attendance swabs were taken from a furuncle and from the anterior nares, and also from the ears and eyelids when indicated by the history or clinical findings. During the later part of the study perineal swabs were also taken. Further swabs were taken during and after treatment, usually at monthly intervals; and also from the relatives of some patients, as described below.

The bacteriological methods were described by Alder *et al.* (1955). Staphylococci were phage-typed by the method of Williams and Rippon (1952).

Treatment.—All the patients were instructed to swab the boil-bearing areas twice a day with a 1 in 3,000 aqueous solution of mercuric chloride. No other treatment was used for the control cases. The test cases were

given an antiseptic cream to apply to the anterior nares two or three times daily, for at least three months. Except for the first few patients (who were treated with "graneodin" ointment), the preparation used was "neobacrin" (neomycin + bacitracin) made up by Glaxo Ltd. in a water-miscible base instead of the standard greasy base. The same cream was applied to the eyelids when eye swabs were positive in the absence of inflammation. Blepharitis was treated with "neocortef" cream (which contained hydrocortisone in addition to the antibiotics). Otitis externa was treated with neocortef drops. During the later part of the investigation hexachlorophane baths (Ayliffe *et al.*, 1959) were prescribed for perineal carriers. The baths were taken daily for one week, then every second day for two more weeks, and then twice weekly for six to eight weeks. Those who could not carry out the bath routine were given "zac" talcum powder (containing 0.3% hexachlorophane) to apply daily to the perineum, buttocks, and trunk.

Results

The results of treatment are summarized in Table I. Of the 23 control cases, 3 were cured and 20 continued to have boils at frequent intervals. Of the 33 test cases, 22 remained free from lesions for at least six months from the beginning of treatment or soon afterwards; five were cured when family sources of reinfection were eradicated; one patient was improved but continued to have occasional boils; and five showed no improvement. One of these failures was a patient with boils on the buttocks who may have been a perineal carrier; but his perineum was not swabbed and hexachlorophane baths were not given.

TABLE I.—*Frequency of Furuncles in the Control and Test Groups of Patients*

	Total Patients	Average Duration of Observation (Months)	Patient-months	Total Furuncles	Furuncles per Patient-month
Controls ..	23	5·4	125	154	1·2
Treated patients:					
During treatment	33	4·7	156	45	0·3
After ,,	19	3·6	68	2	0·03

Clinical improvement was usually apparent soon after the treatment began, even when swabs from the carrier sites remained positive. But some of the patients who were eventually cured continued to have a few boils during the first few weeks of treatment. Recent experience suggests that they might have been cured more rapidly by more intensive treatment of nasal carriage and by the simultaneous use of hexachlorophane baths or powder.

The effect of treatment on the nasal carriage of staphylococci was less impressive than the clinical results. After three months of treatment 5 of 24 patients were still carrying their original strains in their noses, compared with 17 of 20 untreated controls. However, the nasal swabs which stayed positive during treatment usually yielded only scanty growths of staphylococci, and it is evident that the reduction in the load of infection was generally sufficient to prevent a recurrence of furunculosis.

Of 11 nasal carriers whose swabs became negative and whose noses were reswabbed one month or more after stopping treatment, three had again become carriers of their original strains.

Distribution of Furuncles in Relation to Sites of Carriage and Properties of Staphylococci

Of 58 patients, 51 (88%) were nasal carriers of the strains which caused their boils. This level of nasal carriage was similar to that found by Tulloch (1954) in a previous study of furunculosis, and was much higher than the carrier rate of 47% found in 258 healthy adults outside hospital whose noses were swabbed in 1957 and 1958.

Eye swabs from 11 of 21 patients yielded *Staph. aureus*, but all had blepharitis or had previously suffered from it. Of seven patients with present or recent otitis externa, five gave positive ear swabs. Perineal swabs were taken from 27 patients (19 men and 8 women), and 15 (56%) were positive (9 men and 6 women). This figure is probably higher than in the general population, because perineal swabs were at first taken only from patients with boils on the lower part of the body. However, most of the perineal swabs were taken after this examination had been adopted routinely. The perineum was undoubtedly an important carrier site.

Staphylococci of different phage-patterns differed in their distribution among the carrier sites (Table II) and there was a corresponding difference in the areas chiefly affected by boils (Table III). The commonest causes of boils were phage-group II strains and the group I strains 52A/79 and 80, which between them were responsible for 39 of the 58 cases. The 52A/79 strains showed a tendency to cause styes and boils on the upper part of the body, with a similar predilection for the nose as a carrier site to that previously observed in nurses (Alder *et al.*, 1955; Thompson and Gillespie, 1958). Type 80 staphylococci, on the other hand, were more widely distributed in carrier sites, and boils caused by them were seldom confined to the upper part of the body. Group II strains also caused widely distributed lesions, but were carried in the nose more often than on the perineum.

Of the 58 staphylococci which caused furunculosis, 25 (43%) were penicillin-resistant. Thirteen of these were phage-type 80 strains, eight of which were resistant also to streptomycin and tetracycline. A few of the antibiotic-resistant infections were probably attributable to recent contact with hospitals.

Type 80 staphylococci have been responsible for a good deal of serious sepsis in maternity hospitals and general hospitals in Bristol during recent years. Maternity hospitals have been particularly important sources from which these strains have spread into the general population. Recently, after the prophylactic use

TABLE II.—*Nasal and Perineal Carriage of the Staphylococci which Most Often Caused Furuncles*

Phage Pattern	Nose	Perineum	Nose and Perineum
80	6	3	2
52A/79	7	0	0
Group II	17	1	3

TABLE III.—*Distribution of Lesions Caused by Staphylococci of the Types Shown in Table II*

Distribution of Lesions	Phage Patterns		
	80	52A/79	Group II
General	5	1	9
Upper parts of body ..	1	5	8
Lower ,, ,, ,, ..	7	1	2
Total patients ..	13	7	19

of hexachlorophane powder in the maternity hospitals (Simpson *et al.*, 1960; Beryl D. Corner, personal communication), there has been a reduction in the incidence of type-80 staphylococcal infections outside hospital.

Sources of Infection in the Family

Other members of the families of 30 patients had recently suffered from boils. Nasal swabs were taken from 22 families, from 14 of which strains similar to those that had afflicted the patients were isolated from one or more relatives. Five cases of recurrent furunculosis were cured only when family carriage was discovered and treated. The following case was instructive.

Swabs from a boil and from the nose, eyelids, and perineum of a man with a 10-year history of furunculosis yielded a phage-type 42E staphylococcus. His carrier sites were twice rendered free from staphylococci, and his furunculosis cleared up, only to recur within two months. It was then discovered that his wife and two sons were nasal carriers of the same strain. All four were treated with neobacrin nasal cream and hexachlorophane baths. No more boils occurred during the treatment or during a subsequent follow-up period of five months.

Discussion

The detection and eradication of sources of reinfection is of primary importance in the treatment of recurrent boils and styes, and should be carried out before resorting to other methods of treatment. A thorough clinical and bacteriological search for carrier sites on the patient's own body should first be undertaken. The nose and superficial lesions such as blepharitis and otitis externa are often important sources of staphylococci, and so is the perineum, especially when boils are affecting the trunk, buttocks, and thighs. The search for sources of reinfection should extend to other members of the family when necessary.

The clinical success of our treatment was remarkable, in view of the fact that complete suppression of nasal carriage was often slowly and sometimes only temporarily achieved. Subsequent experience has shown that a more intensive treatment, with nasal disinfectant cream applied five or six times instead of twice a day, usually suppresses the carrier state within a few days; and that persistence with the treatment for a further two weeks often cures it permanently, provided that other sites are treated simultaneously. Nevertheless, it may be wise to minimize the risk of recolonization by continuing the treatment for longer than this minimum period. A recent study of the treatment of nasal carriage among in-patients suggests that a nasal cream containing neomycin and chlorhexidine (" naseptin ") may be the agent of choice. Sensitization to neomycin has been reported, but appears to be very rare (Jawetz, 1956; Calnan and Sarkany, 1958). It did not occur in the present investigation, nor in some thousands of in-patients who used nasal cream containing neomycin (Gillespie *et al.*, 1959).

Since staphylococci may be carried on areas of normal skin other than the perineum, and therefore might not be detected by swabbing, our present practice is to prescribe hexachlorophane baths or powder for all patients.

Successful treatment of the staphylococcal carrier state depends largely on the patient understanding the purpose of the treatment and his diligence in carrying it out. He should be given a clear and simple explanation of the nature of staphylococcal carriage and infection. Time spent thus is never wasted. The uninformed patient is almost certain to weary of the treatment and to give it up too soon.

Summary

The treatment of chronic furunculosis by disinfecting sites of staphylococcal carriage was investigated in a controlled trial. Most patients were cured by disinfecting their own carrier sites, but it was sometimes also necessary to eradicate staphylococcal carriage in members of their families.

The nasal carrier site was the most important source of reinfection, but staphylococci from the perineum and from superficial lesions of the skin were also important. Perineal carriage was sometimes associated with boils on the trunk, buttocks, and thighs.

We thank Dr. C. D. Evans and Dr. R. P. Warin for their interest in this work, and for allowing us to study their patients.

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HAEMOPERITONEUM IN VON WILLEBRAND'S DISEASE

CASE OF OVARIAN FOLLICULAR RUPTURE

BY

A. A. SHARP, M.D., B.Sc.
Consultant Pathologist, United Oxford Hospitals

AND

H. ELLIS, M.Ch., F.R.C.S.
Surgical Tutor, Radcliffe Infirmary, Oxford

The term " von Willebrand's disease " is used to describe a somewhat ill-defined haemorrhagic diathesis in which spontaneous bleeding takes place from mucosal surfaces, such as nose, gums, gastro-intestinal tract, urinary tract, and uterus. Only seldom do haemorrhages of deep tissue or joints occur. In most cases there is a definite familial history in which the inheritance is dominant and usually non-sex-linked.

The exact nature of the defect or defects in the haemostatic mechanism in this syndrome is obscure, but laboratory tests show a prolonged bleeding-time in association with normal numbers of circulating platelets. Platelet function is usually normal, while capillary morphology function may be abnormal (Macfarlane, 1941). It is now recognized that in this syndrome low

levels of plasma antihaemophilic globulin (A.H.G.) may be found, and this has led to the use of the term "vascular haemophilia" (Schulman, Smith, Erlandson, and Fort, 1955; Matter, Newcomb, Melly, and Finch, 1956). There is now evidence to suggest that the syndromes named vascular haemophilia and von Willebrand's disease are the same condition (Nilsson, 1959).

Nilsson, Blombäck, Jorpes, Blombäck, and Johansson (1957) have suggested that in this syndrome there is a defect in a plasma factor additional to A.H.G. The Cohn fraction 1–0 of fresh plasma prepared by these workers is capable of shortening the bleeding-time when transfused into patients with von Willebrand's disease, and this effect appears to be independent of the A.H.G. content of the fraction.

The haemorrhagic tendency in this syndrome is usually mild and in most cases only of nuisance value. It is well known that in any given patient there may be a transient increase in the tendency to bleed, and at such times he or she may present as a medical or surgical emergency. Such haemorrhagic episodes rarely require surgical intervention.

Unlike patients with classical haemophilia, those with von Willebrand's disease can sometimes undergo surgical operation without severe secondary bleeding; occasionally and unpredictably, severe secondary haemorrhage does occur post-operatively, particularly from mucosal surfaces, and, once started, is difficult to stop. This latter feature is a serious hazard after removal of tonsils and adenoids and other operations in the nasopharyngeal area in patients with this syndrome.

It is the purpose of this paper to describe an unusual complication of von Willebrand's disease—namely, rupture of ovarian follicular cysts with intraperitoneal haemorrhage on two separate occasions, each requiring surgical intervention.

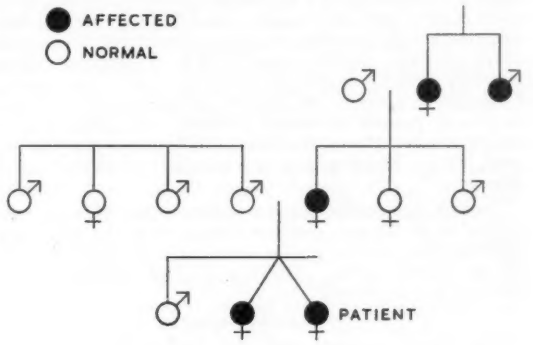
Case History

A schoolgirl aged 16 was admitted as an emergency case to the Radcliffe Infirmary, Oxford, on April 22, 1957, complaining of six hours' severe lower abdominal pain which radiated to the tips of both shoulders. There had been no nausea or vomiting. Her last period had begun 14 days previously, and she was exactly at the mid-point of her menstrual cycle. She had always bruised easily, and had frequent nose bleeds and heavy menstrual periods, which lasted 10 days in a 27-day cycle. She had bled severely after tonsillectomy at the age of 6. Investigations in 1946 and 1960 had revealed a prolonged bleeding-time but normal platelet counts and whole-blood clotting-time.

Family History.—Both the girl's mother and twin sister had a similar haemorrhagic tendency. The mother bruised excessively and had had repeated epistaxes and menorrhagia; a severe episode of the latter had required an emergency hysterectomy. The twin sister's tendency to bleed presented at the age of 5 months with an epistaxis which had necessitated blood transfusion. Since then she had had repeated episodes of melaena. The patient's father and brother had no bleeding-tendency, but her maternal grandmother and great-uncle had shown a definite haemorrhagic tendency; neither had been investigated. The family tree is shown in the next column.

On examination the patient was pale but in good general condition; temperature 100° F. (37.8° C.), pulse 116, blood-pressure 130/180. The abdomen was tender, with marked guarding, particularly below the umbilicus; rebound tenderness was present and the left flank was dull to percussion. Rectally, a fullness could be felt in the pelvis. She was obviously bleeding into the peritoneal cavity, and the relation between the time of onset of her symptoms and her menstrual cycle made rupture of an ovarian follicle the most probable diagnosis.

Operation (H. E.)—The abdomen was explored through a right paramedian incision. There was an extensive haemoperitoneum present, due to a bleeding ruptured right follicular cyst, which was oversewn with catgut. Persistent bleeding from the wound edges was controlled with diathermy and close suturing of the incision in layers with catgut. A corrugated drain was placed in the subcutaneous tissues, being removed next day.



A transfusion of 4 pints (2.2 litres) of blood was given during and after the operation. Recovery was smooth apart from considerable bruising of the abdominal wall and slight oozing of blood from the wound, which continued for some 24 hours. A purpuric rash appeared on the chest and arms on the third post-operative day, and faded two days later.

Laboratory Investigations of Family.—The mother had never shown any abnormality in capillary or clotting function; her bleeding-time and platelet count were invariably normal. The twin-sister's bleeding-time was prolonged to 10–35 minutes, but platelet count and clotting-time were always normal. Her prothrombin consumption index (Merskey) had been found to be abnormal in 1951. Unfortunately neither the patient's mother nor sister would submit to re-examination.

Haematological Investigations.—On admission (April 22): Hb, 75% (11.1 g./100 ml.); bleeding-time (Ivy), 12 minutes; platelets, 180,000/c.mm.; blood film–platelets present in normal numbers; 4 pints (2.2 litres) group O blood transfused. April 23 (12 hours post-operatively): Hb, 73% (10.8 g./100 ml.); blood film—only occasional platelets seen; platelet count—capillary blood 17,000/c.mm., venous blood 15,000/c.mm. Platelet count on April 24–27 and 29 was 15,000, 32,000, 37,000, 32,000, and 52,000/c.mm. respectively. May 11: Hb, 88% (13 g./100 ml.); platelets, 102,000/c.mm.; bleeding-time, 15+ minutes; capillary fragility (Hess), normal; clotting-time, 3, 4½, 5 minutes; prothrombin consumption index (Merskey), 46% (abnormal); antihaemophilic globulin level, 34%; clot retraction normal; capillary morphology normal.

Second Admission

In October the patient was readmitted to the Radcliffe Infirmary because of severe anaemia resulting from menorrhagia.

Laboratory Investigations.—On admission (October 21): Hb, 30% (4.5 g./100 ml.); film, iron-deficiency changes; bleeding-time, 15+ minutes; tourniquet test negative; platelets, 42,000/c.mm. October 28: Hb, 46% (6.8 g./100 ml.); platelets, 48,000/c.mm. October 29: Hb, 87% (12.9 g./100 ml.); platelets, 37,000/c.mm. November 2: Hb, 88% (13 g./100 ml.); platelets, 57,000/c.mm. November 12: platelets, 35,000/c.mm. November 13: Hb, 79% (11.7 g./100 ml.); platelets, 49,000/c.mm. A blood transfusion of 4 pints (2.2 litres) of blood was given on October 28.

Third Admission

The persistently low platelet count suggested that thrombocytopenia might be the explanation of this girl's severe haemorrhagic state. With this in mind, she was referred to Professor L. J. Witts in July, 1958. At this time she was still bruising easily, but her menstrual loss had not been excessive for several months. Her general health was good and clinical examination revealed nothing apart from numerous bruises over her body.

Laboratory Investigations, July, 1958.—Blood picture on July 23: Hb, 102% (15 g./100 ml.); reticulocytes, 2.6%; white count, 7,900 (neutrophils: band 237, segmented 4,266, eosinophils 632, basophils 79, lymphocytes 2,212, monocytes 474); platelets, 100,000/c.mm.; E.S.R. 7 mm./hr. Bone marrow: cellular erythropoiesis active and normoblastic. Considerable increase in number of eosinophils. Megakaryocytes present in normal numbers. Prothrombin consumption index (Merskey), 50%. Antihaemophilic globulin level, 18%. Bleeding-time, 11 minutes. Clotting-time, 2 minutes.

Though the platelet count was low it was by no means as low as on the two previous admissions. The prolonged bleeding-time was far greater than could be accounted for by the platelet count. The low level of antihaemophilic globulin was confirmed.

Fourth Admission

The patient remained well until January 9, 1959, when, once again, she had a serious intra-abdominal haemorrhage. She was admitted to Redhill County Hospital, where laparotomy revealed an extensive haemoperitoneum arising from a ruptured follicle in the right ovary. As there had also been haemorrhage into the stroma of the ovary, oophorectomy was performed. Her recovery was uneventful, with no secondary haemorrhage.

Microscopical examination of the ovary showed several recent haemorrhages into the stroma and rupture of a follicle.

Laboratory Investigations.—January 9: Hb, 70%; clotting-time (Dale and Laidlaw), 3 minutes 2 seconds; bleeding-time (Duke), 15½ minutes; prothrombin index, 65% of normal; platelets present in normal numbers. January 21: Hb, 68%; R.B.C., 3,600,000; clotting-time, 1 minute 55 seconds; bleeding-time, in excess of 17 minutes; platelets, 252,000/c.mm. January 22: bleeding-time, 18 minutes; platelets, 209,500/c.mm.

At the time of writing (November, 1959) no further haemorrhagic episodes had occurred.

Discussion

A minor degree of bleeding from the rupture of an ovarian follicle, normally at the mid-point of the menstrual cycle, is common in normal females, and occasionally severe haemorrhage may take place calling for emergency operation and blood transfusion. In 129 consecutive cases of serious haemoperitoneum admitted to the Radcliffe Infirmary, 10 were due to this cause (Ellis, Griffiths, and MacIntyre, 1958). It is therefore surprising, and unexplained, why this complication has not been found more often in von Willebrand's disease, particularly since menorrhagia is a common feature of this syndrome in women.

There is very little doubt that this patient has an inherited haemorrhagic tendency, transmitted from her mother, which can be classified as von Willebrand's disease. On all occasions when she has been examined her bleeding-time has been prolonged and the platelet count has usually been within normal limits. In addition, her level of plasma antihaemophilic globulin has been low. It has not been possible to assess the effect of plasma fraction 1–0 (Nilsson *et al.*, 1957) on the bleeding-time in order to confirm this diagnosis.

An unusual feature in this patient has been the episode of thrombocytopenia which followed the first operation and subsequent blood transfusion. At the time, this was thought to be the result of transfusion of stored bank blood (Krevans and Jackson, 1955). Whether post-transfusion thrombocytopenia is due to a simple dilution effect or to actual destruction of platelets by some coagulant in the stored blood, or by virtue of an incompatibility of the platelet group of the recipient and the donor blood, remains a mystery. The rise in the number of platelets to a reasonable level before discharge from hospital appeared to confirm the theory of the post-transfusion thrombocytopenia, yet on her second admission to hospital with severe menorrhagia she was again thrombocytopenic. This persisted throughout her stay in hospital, but its significance was again obscured by the necessity for blood transfusion.

A subsequent review of her haemorrhagic state did not reveal any persistence of the thrombocytopenia, and confirmed the diagnosis of von Willebrand's syndrome.

No evidence of a circulation immune platelet agglutinin could be found, and it has not been possible to establish whether this girl has, in fact, episodes of cyclical thrombocytopenia due to menstrual endocrine activity. This latter contingency is unlikely, as normal numbers of circulating platelets were present throughout her stay in hospital consequent on the second episode of intraperitoneal haemorrhage. It is evident from previous reports that relatively low platelet counts may be found in patients who have von Willebrand's disease (Estren, Médal, and Dameshek, 1946).

Whatever the explanation of these thrombocytopenic episodes, it is clear that such profound drops in the level of circulating platelets, occurring in association with an already established haemorrhagic state, might have provoked a more severe and prolonged haemorrhage. Therefore in any patient with a congenital or acquired haemorrhagic tendency of whatever cause requiring transfusion with stored bank blood it is essential to establish the presence or absence of thrombocytopenia before and after transfusion. If such does exist, it is advisable to use fresh platelet-rich (less than 24-hour-old) blood rather than stored blood, if further transfusion is required. For this purpose fresh blood collected into plastic or siliconized containers, using disodium ethylenediamine tetra-acetic acid (E.D.T.A., "sequestrene") as anticoagulant, is preferable to blood collected into the conventional glass bottles containing acid citrate dextrose.

Surgery should be avoided in all the haemorrhagic diatheses if at all possible. In von Willebrand's disease, however, surgery can sometimes be performed without any severe immediate or delayed haemorrhage, although, unfortunately, at present it is impossible to predict by any laboratory test when this will be the case.

There appears on record only one fatal case after surgery in von Willebrand's disease; Little and Ayres (1928) reported a lethal haemorrhage a few hours after splenectomy in this condition, and necropsy revealed an extensive haemoperitoneum though the splenic pedicle was well ligated. Buchanan and Leavell (1956) noted that, in 13 patients with pseudohaemophilia (von Willebrand's disease), 14 surgical interventions had been undertaken — haemorrhoidectomy, appendicectomy, perineorrhaphy, caesarean section, hysterectomy, craniotomy, polypectomy, tonsillectomy (two), circumcision (two), and uterine curettage (three). In several of these

operations bleeding was heavy, but all were successful. These authors also quote six reports of splenectomy in von Willebrand's disease. Only the one case mentioned above resulted in a fatality. (It should be noted that splenectomy has no beneficial effect on this syndrome.)

Horler and Witts (1958), in a series of 20 patients, record one example of a successful gastrectomy for haemorrhage and another of an uneventful nasal polypectomy. One patient bled heavily from an antrum operation and mastoidectomy, and later at appendicectomy; subsequently a gastrectomy was attempted but abandoned because of wound-edge bleeding and visceral haematomata. Another patient, after bleeding heavily as a result of tonsillectomy, underwent an uncomplicated appendicectomy. The patient bled heavily after hysterectomy for menorrhagia. Thus in eight operations on five patients only three were uncomplicated by haemorrhage.

This variation in bleeding tendency at operation has also been noted by Estren *et al.* (1946). In one of their patients laparotomy was abandoned because of profuse haemorrhage from all cut surfaces, yet nine months later this patient underwent abdominal hysterectomy without any abnormal loss of blood. This variability in bleeding tendency is a striking feature in von Willebrand's disease, and occasionally the bleeding-time may return to normal. Irvine and Jones (1957) suggest that advantage should be taken of this fact and elective surgery be performed when the bleeding-time is normal or near normal. It is, however, dangerous to assume that the finding of a normal bleeding-time indicates normal haemostatic function in this syndrome.

Summary

The case is described of a patient with von Willebrand's disease in whom rupture of the ovarian follicle twice led to intraperitoneal haemorrhage.

The nature of this syndrome and its management when surgery is called for are described.

We are indebted to Mr. A. Elliot-Smith and Professor L. J. Witts for permission to publish details of this case, and to Dr. R. Earl and Mr. Normal Pitt, of Redhill County Hospital, for so generously providing the clinical and laboratory data of her admission to that hospital.

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In Victoria the State Cabinet has approved in principle a Bill to allow doctors to give life-saving blood transfusions to children if their parents refuse consent. Similar legislation is already in force in some other Australian States. The Government's action follows the death of a baby late last year after its father refused on religious grounds to consent to a blood transfusion being given to the child. (*Radio Australia News*, April 4.)

Medical Memoranda

Photosensitivity Caused by Promethazine

Promethazine hydrochloride ("phenergan") is related to the phenothiazine group of drugs, and is chemically very similar to chlorpromazine, a drug which has been reported as causing both severe photosensitivity (Cahn and Levy, 1957) and contact dermatitis (Seville, 1956). Promethazine is one of the more potent antihistamines, and for that reason is widely prescribed both for its antiallergic properties and for its sedative effect.

Tzanck *et al.* (1951) published two cases of severe solar dermatitis after the ingestion of phenergan tablets prescribed for contact dermatitis, and Sidi *et al.* (1955) reported on a large number of cases of dermatitis following exposure to summer sunshine after the topical application of phenergan cream. In many of these cases the cream had been given for mild sunburn, and the authors estimated that 50% of all cases of eruptions due to topical medicaments seen by them in 1953 were caused by phenergan cream.

The hot summer of 1959 in the British Isles resulted in many casualties due to heat and sunburn, and three further cases of severe solar dermatitis after the ingestion of promethazine are described.

CASE 1

A housewife aged 28 was 16 weeks pregnant at the time. She had a strong family history of eczema and had herself suffered from atopic eczema of the right wrist and left leg since the age of 14. In August, 1959, she was given phenergan tablets (25 mg. t.i.d.) by her doctor as part of the treatment for this eczema, and a few days later was exposed to hot sunshine. Almost immediately she developed a severe dermatitis of the exposed areas—face, neck, arms, and hands, and both legs below her dress.

The condition was severe enough to warrant admission to hospital, where she was treated with triamcinolone 4 mg. q.i.d., potassium permanganate baths twice daily, and local application of a hydrocortisone alcoholic spray. She was discharged after eight days in hospital, but two weeks later was seen again with a recurrence of the dermatitis after a further prolonged exposure to hot sunshine. Triamcinolone again successfully suppressed the eruption and she was further treated with chloroquine phosphate (250 mg. b.d.) in an attempt to counteract the inflammatory action of sunshine.

When last seen in February, 1960, the eczema was controlled, but sitting by a hot fire tended to cause irritation in the areas previously affected. She had no previous history of photosensitivity and had been able to sunbathe freely. As a child she had suffered from "growing pains" in the legs.

CASE 2

A riding-school mistress aged 40 had no previous history of photosensitivity, but had been investigated three years previously by an allergist for an eczematous rash on the legs, and was found to be sensitive to human hair and horse dander. She had completed a course of specific desensitization to these antigens, but had a slight recurrence of this rash on the legs during a hot period in the early summer of 1958. The rest of that summer had been cold and wet, and she had remained free from further eruptions. In August, 1959, she had a further slight relapse during a spell of hot

weather and was given oral promethazine (phenergan 25 mg. t.i.d.). Four days later, during which time she had been riding in the hot sunshine, she developed a severe weeping eczematous eruption of the face, neck, arms, and hands. Her riding-breeches protected her legs.

She was treated at home with oral triamcinolone, 4 mg. t.i.d., and with topical hydrocortisone alcoholic spray. Her recovery was delayed by a severe furunculosis of the neck and external auditory meatuses which necessitated reduction of the oral corticosteroids and treatment with tetracycline. Not long after her recovery from this episode she was again exposed to hot sunshine while sunbathing and wearing only a bikini type of swim-suit. An immediate recurrence of the dermatitis over the whole body, except for the small area covered by the swim-suit, was treated successfully with the same drugs as previously and with the addition of tetracycline six-hourly to prevent furunculosis. By this time the persistent nature of this condition was recognized and she was given hydroxychloroquine sulphate ("plaquenil" 200 mg. b.d.) in an attempt to prevent further relapses during the hot summer.

Her skin remained clear until February, 1960, when, despite the cold and sunless weather, she had another, less severe, relapse. This again affected her entire body except for the small areas previously covered by her swim-suit, and is considered to have been brought on by sitting in front of a hot fire. She had not been taking antimalarials during the previous three winter months.

She did not recollect having taken phenergan tablets at any time previously, and had never before been affected by hot sunshine. She had had an attack of subacute rheumatism eight years previously.

CASE 3

A plumber aged 32 had no previous history of photosensitivity. While on holiday at the seaside early in August, 1959, he had been stung by a wasp, and, as his hand became swollen, he had consulted a doctor, who gave him six turquoise-blue tablets, later confirmed to have been phenergan. For the next four days—the last of his holiday—he swam and sunbathed in the hot sunshine, and on the fifth day he developed a moderately severe dermatitis of the whole body except for the area covered by his trunks. This was not as severe as in Cases 1 and 2, but it was accompanied by fever and rheumatic-type pains in the wrist and ankle-joints. His E.S.R. was 25 mm. Hg in the first hour (Westergren). He had a past history of two attacks of subacute rheumatism. This latest attack was treated with prednisolone 5 mg. eight-hourly, soluble aspirin 10 gr. (600 mg.) every six hours, and the topical application of hydrocortisone alcoholic spray. The dermatitis and arthritis rapidly subsided but returned two weeks later after a further exposure to sunshine. Unfortunately a follow-up was not possible, as he emigrated soon afterwards to Australia, where the heat-wave of January, 1960, is presumed to have caused him some distress.

COMMENT

These three patients had not previously suffered from any form of photosensitivity, though two had histories of eczematous eruptions. They did not recollect having received promethazine (fortunately the turquoise-blue colour of phenergan tablets is easily recognizable), and none had taken any other drugs immediately prior to the appearance of the eruption which occurred soon after the ingestion of promethazine and exposure to hot sunshine. It is therefore reasonable to assume that this drug was responsible for the lesions described.

All three cases were of the contact eczematous type in the classification of solar dermatitis by Lamb *et al.* (1950). These authors also report evidence of adrenal depression in solar dermatitis as shown by a decreased 17-ketosteroid excretion, and this evidence, combined with the efficacy of corticosteroids and antimalarials in the treatment of this condition, suggests that photosensitivity induced by promethazine is, like lupus erythematosus, a cutaneous manifestation of the rheumatic diathesis. All three cases had previously suffered from some form of subacute rheumatism, and in one (Case 3) a further attack was precipitated by the exposure to hot sunshine after the ingestion of promethazine.

The mechanism by which promethazine initiates this disorder in persons with a rheumatic diathesis is not clear. Adler (1942) suggests a connexion between liver dysfunction and photosensitivity, and though this factor might account for the cases of solar dermatitis reported after the ingestion of chlorpromazine, there is no evidence that promethazine is similarly toxic to the liver. In the light-sensitivity associated with congenital porphyria previous liver damage is often present, but porphyrin excretion was not looked for in these patients, as none had any previous history of light sensitivity, and none had any other symptoms suggestive of an attack of acute porphyria that might have been precipitated by the promethazine. Adamson (1952) made the interesting observation that the initial attacks of any contact dermatitis are usually precipitated by conditions of heat, either solar or artificial. In this event the ingested drug behaves similarly to the topical application of phenergan cream described by Sidi *et al.* (1955). Possibly promethazine is directly toxic to the adrenal cortex in some individuals.

Sidi *et al.* stress the chronic nature of the photosensitivity in this condition and state that it may continue for months or even years after the initial sensitization, with relapses at every exposure to sunshine or even to bright light. The subsequent history of Cases 1 and 2 emphasize this chronic tendency. These people had relapses even in winter when sitting by a hot fire.

Whatever the cause, it would seem advisable, during hot weather, to prescribe some antihistamine other than promethazine to persons who are known to suffer from eczema in any form or who have a tendency towards rheumatism. It is not unlikely that many cases of eczema of the face and neck, at present diagnosed as contact dermatitis of unknown cause, would be found on inquiry to have been taking promethazine and who were subsequently exposed to a hot fire or to sunshine.

I thank Dr. Ian Martin-Scott for permission to include details of Case 1, admitted to the West Herts Hospital, Hemel Hempstead, under his care, and for advice in the presentation of this paper.

R. G. D. NEWILL, M.B., B.S.,
General Practitioner,
Chipperfield, Hertfordshire.

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Reviews

THE SURGEON AND THE CHILD

The Surgeon and the Child. By Willis J. Potts, M.D. (Pp. 255+ix; illustrated. 52s. 6d.) Philadelphia and London: W. B. Saunders Company. 1959.

This book is a rarity among medical writings because of the way in which it conveys the author's personality. Dr. Potts is one of the brilliant group of American paediatric surgeons who have done so much in recent years to improve our results in operations on the young. As he himself says, "Twenty years ago the rare paediatric surgeon was looked on as a peculiar person who, for some reason known only to himself, chose to operate on little people. Need and demand have changed this viewpoint."

Those who have the good fortune to know Dr. Potts personally recognize him not only as one of the most brilliant and original technicians of our time but as the possessor of a deep human sympathy not always to be found among users of the scalpel. His qualities of mind are shown early in the book, when he has the daring to discuss a subject which medicine, law, and religion have up to now avoided—what should be done with the utterly hopeless newborn child. He gives three examples of solutions to this dreadful problem, and leaves it at that.

As the title of the book suggests, he makes no attempt at the impossible task of covering the whole field of the surgery of childhood, but writes of what he knows with a welcome absence of the scissors-and-paste method so obvious in most attempts at comprehensive textbooks. His personal opinions, as with all such original characters, are strong. It is interesting that with his unsurpassed brilliance in cardiac surgery he has a deep distrust of the fashionable form of anaesthesia which consists in keeping a not-always-easy balance between paralysing drugs and their antidotes: "Curare can make any anaesthesia look good. What does not show is the danger of inadequate respiratory exchange and its fearsome consequences."

There are many designers of surgical instruments, but to few is it given to make a contribution such as that unlikely-looking saw-toothed grip, shown on p. 99, which has so lightened the anxieties of those who deal with the various fragile tubes in the infant body; prophecy is dangerous, but it is possible the Potts clamp will survive as long as the Spencer Wells artery forceps.

One of the few criticisms of this all-too-short book is that Dr. Potts has not given in full the substance of one of the most impressive addresses ever delivered at the Royal College of Surgeons, the 1958 Moynihan Lecture on "Respiratory Emergencies in the New Born." Such a masterly statement of the disasters that may afflict normal infants and the theory and practice of countering them should not be left in the comparative obscurity of the *Annals of the Royal College of Surgeons* (1958), **23**, 275.

DENIS BROWNE.

MINOR HAND INJURIES

The Care of Minor Hand Injuries. By Adrian E. Flatt, M.A., M.D., F.R.C.S. Foreword by Carrol B. Larson, M.D. (Pp. 266; illustrated. 71s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

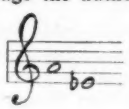
The hand plays such an important part in the human economy, for we are all in some degree manual workers, that it is not surprising to find quite a number of books devoted to its injuries and diseases. *Minor Hand Injuries* by Adrian E. Flatt is perhaps unique in that the author, who trained and acquired his earlier experience in this country, is now attached to an American university. In his foreword Dr. Carrol Larson pays a graceful compliment to the author and to his country of origin when he quotes "To know the origin of a book is often to know its value."

It has frequently been said that in the care of the hand there is no such thing as "minor" surgery, but in his preface the author counters this by explaining that he used the word "to imply a relatively small amount of tissue damage, out-patient treatment, and freedom from post-operative complications." Although this somewhat begs the question, for the avoidance of complication is what makes this branch of surgery so important, we are prepared to accept it.

It is of interest to see how the introduction of the sulpha drugs and the antibiotics has changed the whole balance of textbooks on this subject. Previously they were largely concerned with various infections and their spread, whereas we now find that the name of Kanavel is not mentioned nor is his classic work on hand infections included in the works for "recommended reading"—*sic transit gloria mundi.*

There is perhaps nothing very novel or controversial in this new volume, but the text in general is written with great clarity and common sense. Wise judgment, arising from wide experience, is to be found in every chapter, as an example from the chapter on burns will show: "after grafting use of the hand is important, and it should be used to the point of discomfort for ordinary domestic and occupational tasks. Such use will frequently produce a better result more quickly than infrequent systematized occupational or physiotherapy." It is pleasant, too, to see in an American book a considerable number of references to books and papers of British origin, but this is to be expected from the author's background.

The very numerous and helpful illustrations are beautifully reproduced and indeed are an example of what medical illustration can be at its best. The publishers are to be congratulated on the general format of the book, which is very attractive. We note that on the dedication page the author somewhat facetiously signs himself



NORMAN C. LAKE.

AIDS TO MEDICAL BIOCHEMISTRY

A Guide-Book to Biochemistry. By Kenneth Harrison. (Pp. 150+viii. 17s. 6d.) London: Cambridge University Press. 1959.

A Biochemical Approach to Pathology. By M. J. R. Dawkins, M.B., B.Ch., M.R.C.P., and K. R. Rees, M.Sc., Ph.D. (Pp. 128+vii; illustrated. 18s.) London: Edward Arnold (Publishers) Ltd. 1959.

The increasing importance of biochemical concepts in pathology and medicine, and the increasing complexity of these concepts, place a heavy burden on the teacher who must try to reconcile structure with function. These two books give an extremely readable account of the essential principles involved, and are to some extent complementary to one another.

The first book, by Dr. Kenneth Harrison, provides a lucid description of basic biochemical mechanisms and is very easy to read. No practical details are, of course, included, but sufficient detail is given of chemical

formulae to permit a detailed description of enzyme mechanisms. The presentation follows to some extent the pattern of Professor Baldwin's earlier *Dynamic Aspects*, which also originated in the Cambridge School of Biochemistry, but is in a more condensed form. The very short chapter on control of metabolism is stimulating, and suggests the hope of future progress.

The second book, by Dr. Dawkins and Dr. Rees, reads rather like a continuation of the first, and is particularly concerned with the nature of metabolic disturbances from the cellular angle, with special reference to the effects of toxins and of deficiency states, both congenital and acquired. Both authors work at University College Hospital Medical School, and their outlook no doubt reflects the interest in the subject of Sir Roy Cameron to whom the book is dedicated. Current knowledge of the basic metabolic defects in disease is well described in this book, and the authors do not hesitate to point out fields where knowledge is incomplete.

Both books can be cordially recommended to the general reader in the medical field who is interested in the possibility of establishing the nature of basic biochemical disturbances in disease. They form not only an extremely useful guide to the enormous literature on this subject, but also make some important contributions in their own right.

N. F. MACLAGAN.

DEDICATED TO SCHICK

Current Problems in Allergy and Immunology. Papers Dedicated to Béla Schick on the Occasion of his 80th Birthday. Edited by William Kaufman. (Pp. 992+xxiv; illustrated. Sw. Fr. 60; $14.40.) Basle, New York: S. Karger. 1959.

This volume is dedicated to Dr. Béla Schick on the occasion of his eightieth birthday, and it is pleasing to know that Dr. Schick, born in Hungary, trained in Graz, Austria, is still actively interested in medicine in America, where he went at the age of 46. Among his other appointments he has been professor of children's diseases at Vienna; paediatrician to the Mount Sinai Hospital, New York; clinical professor of diseases of children, Columbia University; and director of the paediatric department, Sea View Hospital, New York.

Dr. Schick is known the world over for the test of diphtheria immunity which bears his name. Almost equally well known and of equal importance was his work with that of Clemens von Pirquet on serum sickness. Their classic contribution "Serumkrankheit"—serum sickness—appeared in 1905 (an English translation by Dr. Schick appeared in 1951), and in the following year von Pirquet coined the word "allergy." Serum sickness has been described as the cornerstone of allergy. The editor has therefore collected some 56 articles from 100 medical scientists and physicians from all over the world on topics in allergy and immunology. Five of these articles are in German, three in French, and the remainder in English. Articles by contributors from Great Britain are on diphtheria toxin by Professor Marrack; the immunological basis of carcinogenesis by Professor Green; lobsters, lymph, and histamine-liberation by Professor Paton; the histological criteria of hypersensitivity by Pagel and Triep; experimental allergic lesions in animals by Gell; while Carl Prausnitz writes on the past, present, and future of allergy.

Many European countries are represented as well as Australia and South Africa, but the majority of the contributors are from North America. This latter is not surprising, for Dr. Schick's work and personality have undoubtedly had a considerable influence on the study of allergy in the land of his adoption.

The subjects vary widely, with the emphasis, as one would expect, on aspects of allergy affecting children as well as on the experimental side of allergy. Side-by-side are such diverse subjects as an appraisal of serological reactions in rheumatoid arthritis by Sulkin and Pyke, and food-induced allergic illness in children by Kaufman; liver disease and antibody formation by Havens, and musculo-skeletal allergy in children by Randolph; the influence of bacterial polysaccharides and steroids on the passive arthus phenomenon in guinea-pigs by Jaques, Bein, and Meier, and emotional factors in allergy with special reference to asthma by Weiss.

All the articles in this volume have already appeared in the *International Archives of Allergy and Applied Immunology* in the Béla Schick Anniversary Numbers. All who are interested in this branch of medicine and who have not read them in the *International Archives* will find many articles of interest in this excellently produced volume.

D. A. WILLIAMS.

EXPERIMENTAL ENCEPHALOMYELITIS

Allergic Encephalomyelitis. Proceedings of a Symposium: Experimental "Allergic" Encephalomyelitis and its Relation to other Diseases of Man and Animals. Edited by Marian W. Kies, Ph.D., and Ellsworth C. Alvord, Jr., M.D. (Pp. 576+xiv; illustrated. £5 2s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The aetiology of the demyelinating diseases, the commonest of which is disseminated sclerosis, remains unknown, but some workers think that they may have an allergic basis comparable with the experimental allergic encephalomyelitis that may be produced in some animal species.

This beautifully illustrated volume contains the proceedings of a conference held at Bethesda, Maryland, in October, 1957, and attended by many workers on the problem. The book reproduces essentially the papers as read to the conference with the subsequent discussions, but some remarks have been added later and these are indicated in the text. From the standpoint of the clinical neurologist and neuropathologist there are a number of papers of great interest, in particular the account of encephalomyelitis after rabies inoculation in Japan, the paper by Raymond Adams comparing the morphology of the human demyelinating diseases and the experimental disease in animals, and the summary and concluding remarks by Alvord. In addition there are a number of papers discussing the technical aspects of the production of experimental encephalomyelitis, in particular the chemical substances involved, and others on the immunological aspects of the experimental disease.

These papers show clearly the complexities of the problem, but more particularly indicate the contributions likely to be made in the discovery of the aetiology of neurological diseases by scientific disciplines far removed from clinical neurology and orthodox neuropathology.

J. W. ALDREN TURNER.

ENDOCRINOLOGY OF REPRODUCTION

Recent Progress in the Endocrinology of Reproduction. Proceedings of a Conference held in Syracuse, New York, June 9–12, 1958. Edited by Charles W. Lloyd. (Pp. 532+xi; illustrated. $12.) New York, London: Academic Press. 1959.

This book represents the proceedings of a special conference held in Syracuse, New York, in June, 1958. Twenty-three papers given by anatomists, physiologists, biochemists, and endocrinologists, together with extensive bibliographies and attendant discussions, are reproduced in full. The names of the contributors make a formidable list of internationally known experts, drawn from Australia, Canada, Germany, and Great Britain, as well as various parts of the U.S.A. Each summarizes knowledge in his particular field and indicates the results of his own researches. The subjects include the endocrine function of the placenta, the metabolism of steroid hormones, the excretion levels of sex hormones measured by latest methods, the physiology of lactation, and the effect of temperature on fertility. A main theme of the conference, however, was endocrine relations—the neuro-hypophysial control of ovulation, sperm transport, pregnancy, parturition, and lactation. So much so that Sir Solly Zuckerman, in his closing remarks, said that "endocrinologists step in where . . . some neurologists would fear to tread." He also commented on the temptation to generalize with a view to presenting a logical if incompletely proven picture of a problem.

Be this as it may, it remains important for those outside a specialized field of research to have a working concept of progress in other spheres. This is as true for clinicians who wish to practise logically rather than empirically as it is for research workers. And if this book aims primarily to exchange knowledge between one group of experimentalists and another, it also offers the gynaecologist and clinical endocrinologist an easy method of keeping abreast of modern theoretical knowledge. Despite the lapse of time since the conference, the material can still be described as new. It offers a mine of information for all workers in the field of human reproduction and sex physiology.

T. N. A. JEFFCOATE.

HORMONES

Hormone. Einführung in ihre Chemie und Biologie. By Dr. Oldřich Hanč. (Pp. 633+xi; illustrated. DM. 40.) Jena: VEB Gustav Fischer Verlag. 1959.

This book on the hormones, written in German, is undoubtedly a credit to the Research Institute for Pharmacy and Biochemistry, Prague, where its author works. My limited knowledge of the German language unfortunately does not permit me to express an opinion on its literary merit, but as a scientific treatise it certainly deserves to be regarded as a valuable contribution to works on endocrinology. All aspects of the hormones are considered—their discovery, function, chemistry, estimation, therapeutics, and so on—but the sections on chemistry in particular appear to be notably detailed and complete. As befits their importance in modern endocrinology, the steroid hormones receive the most extensive attention, almost exactly half of the 633 pages of the book being devoted to them.

After each chapter there is an extensive list of references, usefully divided into general and special papers, which appears to be remarkably up to date for a textbook and refreshingly non-parochial in origin. There is a good index, and the general standard of production is high. This book can confidently be recommended to those readers familiar with the German language.

G. I. M. SWYER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Diabetic ABC. A Practical Book for Patients and Nurses. By R. D. Lawrence, M.A., M.D., F.R.C.P.(Lond.). Twelfth edition. (Pp. 82+x. 5s. 6d.) London: H. K. Lewis and Co., Ltd. 1960.

Poisons and T.S.A. Guide for Pharmacists in Retail and Hospital Practice. Sixth edition 1960. Published by direction of the Council of the Pharmaceutical Society of Great Britain. (Pp. 75. 7s. 6d.) London: Pharmaceutical Press. 1960.

Dermatologie und Venerologie. Einschliesslich Berufskrankheiten Dermatologischer Kosmetik und Andrologie. Edited by Professor Dr. H. A. Gottron and Professor Dr. W. Schönfeld. Volume IV: ***Erbkrankheiten Fehlund Neubildungen Hautkrankheiten Besonderer Lokalisation und Besonderer Lebensalter.*** (Pp. 1,174+xxiv; illustrated. DM. 290.) Stuttgart: Georg Thieme Verlag. 1960.

The Divided Self. A Study of Sanity and Madness. By R. D. Laing. (Pp. 240. 25s.) London: Tavistock Publications. 1960.

Life in the Twenty-first Century. The Fantastic World of the Immediate Future as Predicted by 29 of Russia's Leading Scientists. Edited by M. Vassiliev and S. Gouschev. (Pp. 231; illustrated. 21s.) London: Souvenir Press. 1960.

Antikoagulantien in der Chirurgie. By H. A. Thies and J. Oeri. (Pp. 54. Sw. fr. 6.50.) Basle and Stuttgart: Benno Schwabe and Co. 1960.

African Homicide and Suicide. Edited by Paul Bohannan. (Pp. 270+xix. 48s.) Princeton, N.J.: Princeton University Press. London: Oxford University Press. 1960.

Miscellaneous Notes. (Sixth Series.) By F. Parkes Weber, M.D., F.R.C.P., F.S.A. (Pp. 10. 3s.) London: H. K. Lewis and Co., Ltd. 1960.

Psychiatric Dictionary. By Leland E. Hinsie, M.D., and Robert Jean Campbell, M.D. Third edition. (Pp. 788+ix. £7.) New York and London: Oxford University Press. 1960.

Surgery as a Human Experience. The Psychodynamics of Surgical Practice. By James L. Titchener, M.D., and Maurice Levine, M.D. (Pp. 285+xxx. 48s.) New York and London: Oxford University Press. 1960.

The Jaws and Teeth of Primates. Photographs and Commentaries. By W. Warwick James, O.B.E., F.R.C.S., M.Ch., F.D.S., F.L.S. (Pp. 328+xii. £5 5s.) London: Pitman Medical Publishing Co., Ltd. 1960.

Periodizität in der Psychopathologie (Neuro- und Allgemeinpathologie). By Dr. E. Menninger-Lerchenthal. (Pp. 310+vii. 94s.) Vienna, Bonn, Berne: Wilhelm Maudrich Verlag. 1960.

Patologie General y Fisiopatologia. By Enrique Romero. In two volumes. (Pp. Vol. I: 1,184; Vol. II: 1,222; illustrated.) Madrid: Distribuido por Editorial Paz Montalvo. 1960.

La Méningite Tuberculeuse et son Traitement. By Jean Fouquet. (Pp. 236; illustrated. NF. 30.) Paris: G. Doin et Cie. 1960.

An Introduction to the Anaesthesia of Laboratory Animals. By Phyllis G. Croft, Ph.D., M.R.C.V.S. (Pp. 31; illustrated. 3s. 6d.) London: Universities Federation for Animal Welfare. 1960.

Mental Subnormality: Subnormality and Severe Subnormality. By W. Alan Heaton-Ward, M.B., Ch.B., D.P.M. (Pp. 64; illustrated. 6s.) Bristol: John Wright and Sons, Ltd. 1960.

Klinische Neuroradiologie. Edited by Professor Dr. Kurt Decker. With eight contributors. (Pp. 507+xvi; illustrated. DM. 230.) Stuttgart: Georg Thieme Verlag. 1960.

Essays and Studies 1960. Volume 13 of the New Series. Collected for the English Association by M. St. Clare Byrne. (Pp. 114. 13s. 6d.) London: John Murray. 1960.

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THE SPIROLACTONES

The pathogenesis of cardiac and other forms of oedema has inspired much experimentation during the past fifty years, without any firm conclusions having been reached. Because aldosterone has a powerful effect in promoting retention of sodium, it is natural to suspect that overproduction of this hormone may be an aetiological factor in formation of oedema. An increased excretion of aldosterone has been detected in some cases of ascites and oedema due to cirrhosis of the liver and in some cases of cardiac oedema.

It was a natural step from this concept to try to find compounds antagonizing the effect of aldosterone on the kidney. Earlier success in the discovery of other so-called antimetabolites—such, for instance, as aminopterin—gave encouragement that this would prove possible. Accordingly C. M. Kagawa and colleagues[1] undertook this task, and in 1957 they announced the discovery of a new chemical series of compounds, the 17-spirolacto-steroids, which antagonize the effects of aldosterone not only in animals but also in the human subject, both normal and oedematous. Several compounds of this type have been studied; the most satisfactory so far has proved to be the compound designated by the makers SC-9420. This is better absorbed when given by mouth than some of the earlier spirolacto-steroids tried. To this compound the official name spironolactone has now been given, and it has recently been made available for general clinical trial under the trade name "aldactone."

There is considerable evidence that this substance does indeed antagonize the effects of aldosterone on the renal tubules. Thus it has been found to have little effect on normal subjects who are on a high-salt diet, when production of aldosterone is minimal, whereas the same subjects on a low-salt diet, when production of aldosterone is high, may show a good diuresis. Patients with Addison's disease, who may be presumed to produce little aldosterone, showed little effect from the spirolactone, but when these same patients are maintained on either desoxycorticosterone or on aldosterone a significant effect on electrolyte excretion is obtained, potassium being retained and sodium lost.[2 3]

Then again potassium loading, which stimulates production of aldosterone, also enhances the effect of spironolactone.[4] The typical effect is, in fact, the reverse of that produced by aldosterone, and experimental evidence is in general consistent with the view that these spirolactones have no action on the kidney except by virtue of inhibiting the effects of the salt-retaining steroids.

The primary purpose of these compounds was for the treatment of oedema, especially the forms resistant to the usual therapeutic measures, in which production of aldosterone was likely to be raised. In such subjects diuretics such as chlorothiazide and the newer hydroflumethiazide may cause a considerable drain of potassium in addition to the chloride and any sodium. C. J. Edmonds and G. M. Wilson[5] have shown that this effect is particularly likely to occur with hydroflumethiazide when the patient is on a low-salt diet, as are most patients with heart disease undergoing sodium diuresis. The loss of potassium in such circumstances, they showed, can be considerably reduced by simultaneous administration of a spirolactone. Sheila Sherlock and her colleagues[6] have reported that a particularly effective combination for the treatment of resistant ascites is spironolactone, chlorothiazide (for two days only), and mannitol—the last being an osmotic diuretic.

What is known about the pharmacology of these compounds suggests that their potency in any patient with cardiac disease or cirrhosis of the liver will depend mainly on the extent to which that patient secretes aldosterone. V. Cejka and colleagues[7] have recently reported beneficial effect in a case of resistant cardiac oedema with high excretion of aldosterone. But the conditions which determine secretion of aldosterone are not yet adequately understood, and it is accordingly not possible to predict clinically which cases of sodium retention will respond to the drug. Nor are aldosterone assays of any kind yet feasible as a routine guide to treatment.

A study of the effects of spironolactone in relation to other diuretics has been made by Edmonds.[8] He divided patients with chronic oedema or ascites into three groups, according to their response. The first group were those in whom both hydroflumethiazide and mersalyl caused a large rise in excretion of

[1] Kagawa, C. M., Cella, J. A., and Van Arman, C. G., *Science*, 1957, **126**, 1015.
[2] Liddle, G. W., *Arch. intern. Med.*, 1958, **102**, 998.
[3] Ross, E. J., and Bethune, J. E., *Lancet*, 1959, **1**, 127.
[4] Taylor, F. F., and Faloon, W. W., *J. clin. Endocrinol.*, 1959, **19**, 1683.
[5] Edmonds, C. J., and Wilson, G. M., *Lancet*, 1960, **1**, 505.
[6] Shaldon, S., McLaren, J. R., and Sherlock, S. ibid., 1960, **1**, 609.
[7] Cejka, V., de Vries, L. A., and Borst, J. G. G., ibid., 1960, **1**, 312.
[8] Edmonds, C. J., ibid., 1960, **1**, 509.

sodium and chloride with little change in excretion of potassium. In this group the spironolactone had little action. The second group consisted of those cases in which these diuretics increase excretion of chloride with associated increase of potassium output. Spironolactone by itself increased excretion of sodium in some of these cases, and when given together with hydroflumethiazide reduced considerably the loss of potassium which would otherwise have occurred. The third group was composed of those cases in which neither mersalyl nor hydroflumethiazide caused appreciable diuresis of either sodium or potassium. In this group the spironolactone had no effect. These results are in conformity with the general view that secretion of aldosterone is raised in the second group and that its action is being inhibited by the spironolactone. Using spironolactone together with either mersalyl or hydroflumethiazide, Edmonds has been able to maintain patients of the second group satisfactorily for many weeks without further trouble from loss of potassium.

On page 339 of the *Journal* this week a report reaching somewhat similar conclusions is published from New Zealand. The authors, Drs. R. O. Farrelly, R. N. Howie, and J. D. K. North, have studied seven patients with cardiac oedema resistant to other modes of therapy. Hydrochlorothiazide caused the usual increase in excretion of both sodium and potassium, but excretion of the former was greatly diminished by the fourth day. When spironolactone was added to the hydrochlorothiazide a further diuresis of sodium was achieved, but excretion of potassium fell. Though all the patients were in negative potassium balance on hydrochlorothiazide, this was converted to a positive potassium balance by the spironolactone.

There is thus a general agreement that the spironolactone can be of value in preventing wastage of potassium during orthodox diuretic therapy. Farrelly and his colleagues have concluded provisionally that this action is of more clinical value than any diuresis of sodium the drug may produce. They point out that, though loss of potassium can usually be combated by giving potassium chloride by mouth, this form of potassium therapy is not acceptable to all patients, and the spironolactone may be preferable for some. It appears to be non-toxic even in large doses, and if any sensitivity reactions do occur they are likely to be rare.

The precise place of the spirolactones in the therapy of resistant oedema is not likely to be settled for a while. The New Zealand authors think they may be less effective in eliminating the water of oedema fluid than the sodium. Further careful study will be needed before their real value can be correctly assessed, but it is already clear that in this group of aldosterone antagonists we have compounds which offer a new mode of attack on both the aetiological and the therapeutic problems of chronic oedema.

A.I.D.

In expressing its wish to discourage the practice of artificial insemination by a donor (A.I.D.) the Government committee which reported[1] last week probably reflected the opinion of most people in Great Britain who have thought about the matter. It is not a procedure that has found many advocates in the medical profession, and it has, on the contrary, met with much criticism. The B.M.A.'s memorandum of evidence[2] to the committee commented thus: "A.I.D. would not appear to contravene any of the accepted principles of scientific medicine; nevertheless there is a substantial body of opinion in the profession which regards this practice as an undesirable one, and many doctors are absolutely opposed to it on moral and religious grounds." The committee's report reinforces this when addressing itself directly to members of the medical profession: "We hope that we leave neither prospective parents nor any doctors under any misapprehension as to the view which we take. We think the practice most unwise and a grave injustice (whether regarded as a real or only a potential danger) to the intended child."

General interest in A.I.D. was first aroused in Britain at the end of the war after publication of an article by Mary Barton and colleagues.[3] The subject was debated in Parliament and the Press, and in consequence the Archbishop of Canterbury set up a commission to inquire into it. With one dissentient its members condemned A.I.D. as wrong in principle and contrary to Christian standards.[4] But a small demand for it continued to exist, and in selected cases was met by a few medical practitioners acting in accordance with carefully devised criteria. Then in 1958 public concern was again aroused by a divorce case in Edinburgh,[5] in which the judge decided that

[1] *Report of Departmental Committee on Human Artificial Insemination*, Cmnd. 1105, H.M.S.O. (5s. 6d.). See summary at p. 379.
[2] *Brit. med. J. Suppl.*, 1959, **1**, 289.
[3] Barton, M., Walker, K., and Wiesner, B. P., *Brit. med. J.*, 1945, **1**, 40.
[4] See ibid., 1948, **2**, 523.
[5] Ibid., 1958, **1**, 229.
[6] Glass, D. V., *J. roy. statist. Soc.*, 1960, **123**, 174.
[7] Hajnal, J., ibid., 1960, **123**, 182.
[8] Bartholomew, G. W., *Eugen. Rev.*, 1958, **49**, 187.
[9] Jackson, M. H., *et al.*, ibid., 1957, **48**, 203.
[10] Schellen, A. M. C. M., *Artificial Insemination in the Human*. Amsterdam and London, 1957

A.I.D. without the husband's consent did not constitute adultery according to the law of Scotland. It is worth recording the somewhat unusual nature of these and other causes of interest among the general public, because in practice A.I.D. has been so infrequently carried out that very few people have any personal knowledge of it at all. The number of children born in this country during the last two decades as a result of A.I.D. (including cases of mixed semen from donor and husband) is about 1,100, according to the Government report, and out of this total three practitioners have been concerned with about 1,000 births. Since one of the fears expressed about A.I.D. is that it could lead unwittingly to marriages between half-brothers and half-sisters, the number of children so far born by it is reassuringly small. In fact, on a number of assumptions which would have the effect of providing for a greater number of A.I.D. births per year than have occurred, it has been recently estimated that the chance of such marriages taking place would be exceedingly low—probably not more than one marriage in 100 years.[6 7]

The main basis for a medical practitioner's responding to his patient's request for A.I.D. is that the procedure is a therapeutic measure,[8] though this may be interpreted in the rather general sense that it can bring happiness to a man and woman who will otherwise lack it. The people who seek the doctor's aid, too, would normally seem to regard it in the same light. It is therefore interesting to see that the committee does not accept this view. In the first place, though some evidence has been published,[3 9 10] there seems to be no thorough report on a substantial number of followed-up cases, showing what the effects of A.I.D. are, apart from data on the frequency with which conception resulted. There are obvious difficulties—in keeping track of the patients, in assessing the consequences to them, in making a comparison with controls. It is evident that the committee found itself in a quandary here, and commented: "We have particularly borne in mind that the practitioners who do recommend A.I.D. are, for the most part, unaware of the eventual outcome of their cases." It then states its views that "A.I.D. is liable to endanger the relationship between husband and wife"; "A.I.D. must be accounted a handicap for the child so conceived"; the practice of donating semen "appears to indicate a certain irresponsibility"; and "certain aspects of the practice of A.I.D. are outside the province of a medical practitioner."

Among the few changes in the law which the committee recommends, the most notable are, first, that a wife's acceptance of A.I.D. without her husband's consent should be made a new ground for divorce, and, secondly, that the birth of a child by A.I.D. to which husband and wife consented should be a bar to proceedings for nullity of the marriage on grounds of impotence. On the main issue of the legality of A.I.D. itself, the recommendation is that the law should be left as at present, for if the practice were made illegal it might fall into the hands of unscrupulous people. As the committee observes, "In so far as the practice does continue we are unanimous that it is better it should remain in the hands of medical practitioners." But both the majority who sign the report and the minority who dissent from it agree that A.I.D. should not be encouraged.

RENAL-ARTERY STENOSIS

Since H. Goldblatt's[1] original experiments, producing hypertension in animals by clamping the renal artery, and since A. M. Butler's[2] first report of restoration of the blood-pressure to normal in man after nephrectomy for pyelonephritis, unilateral renal disease has been recognized as a rare but treatable cause of hypertension. Originally the lesion looked for was unilateral pyelonephritis, and it is only recently that attention has been increasingly focused on arterial lesions of the kidney. H. W. Smith,[3] writing in 1956, doubted whether the discovery of renal arterial lesions, generally of an occlusive nature, by aortography would mark any great advance in the treatment of hypertension, since arterial anomalies conducive to hypertension might be expected to be rare. He also warned against attaching undue importance to minor abnormalities of the renal vascular tree, advocating the use of unilateral clearance methods in the full assessment of cases of hypertension with suspected unilateral renal disease. More recently an increasing number of authors have reported alleviation of hypertension by operations that correct a stenosis or remove the affected kidney.[4–7] Now Professor W. S. Peart and his colleagues report in the opening pages of the *Journal* this week a series of cases of renal-artery

[1] Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W., *J. exp. Med.*, 1934, **59**, 347.
[2] Butler, A. M., *J. clin. Invest.*, 1937, **16**, 889.
[3] Smith, H. W., *J. Urol. (Baltimore)*, 1956, **76**, 685.
[4] Poutasse, E. F., *Circulation*, 1956, **13**, 37.
[5] DeCamp, P. T., and Birchall, R., *Surgery*, 1958, **43**, 134.
[6] Owen, K., *Postgrad. med. J.*, 1959, **35**, 645.
[7] Robertson, J. I. S., *Proc. roy. Soc. Med.*, 1960, **53**, 375.
[8] Oster, J., *Acta med. scand.*, 1947, **128**, 42.
[9] Dollery, C. T., Shackman, R., and Shillingford, J., *Brit. med. J.*, 1959, **2**, 1367.

stenosis in some of which nephrectomy or reconstructive surgery was followed by restoration of the blood-pressure to normal.

It is difficult at present to assess the incidence of renal-artery stenosis as a cause of hypertension. As yet there are no generally accepted methods of diagnosing it clinically, and in routine necropsies of hypertensive patients partial obstruction of a renal artery might well be missed unless specifically looked for. In addition, functionally significant stenosis of a renal artery can be confirmed only by demonstrating a pressure gradient across a region of arterial narrowing at operation. Finally, the proof that the stenosis is the cause of the hypertension can only follow permanent return of the blood-pressure to normal after arterial reconstruction. It was previously estimated that unilateral renal lesions amenable to surgery, usually due to pyelonephritis, accounted for not more than 2% of all hypertensive patients.[3] But Peart and his colleagues report the finding of renal-artery stenosis in 10 out of 160 patients with severe hypertension investigated by renal aortography, giving an incidence of 6 to 7%, suggesting that this lesion is not rare.

The commonest cause of renal-artery stenosis is atherosclerosis, either sclerosis of the renal artery itself or an atherosclerotic plaque in the aorta occluding the mouth of the renal artery, but a wide variety of other causes have also been described. Congenital lesions include stenosis of the renal artery itself, abdominal coarctation, renal arterial aneurysm, and multiple renal arteries with stenosis and occlusion of one or more. Of the acquired lesions, besides atherosclerosis, thromboangiitis, idiopathic thrombosis, embolism, syphilis, trauma, extrinsic tumour, and extrinsic bands have all been reported.

The diagnosis can be made only after extensive special investigation, since no particular clinical features distinguish these patients from others with severe hypertension. P. T. DeCamp and R. Birchall[5] emphasize that extremes of age may rouse suspicion of the diagnosis, old patients developing hypertension being more likely to have a renal arterial lesion as part of widespread arterial disease, while in children (and even infants) congenital arterial lesions may be detected as causing the hypertension. A more positive diagnostic feature, stressed by Peart and colleagues, is the presence in some of these patients of a murmur either just to one side of the mid-line over the upper abdomen or posteriorly in the renal angles. Direct auscultation at operation has shown that the murmur is loudest over the site of stenosis in the renal artery. Occasionally, when a renal artery is suddenly occluded by an embolus or other cause, the symptoms may be acute, with sudden pain in the loin, fever, and leucocytosis. Proteinuria may or may not be present and is therefore unhelpful in diagnosis. Similarly polyuria[8] and loss of potassium[9] reported in some cases do not appear to be common accompaniments. The affected kidney may be slightly smaller than the other on plain *x*-ray examination.

The two most important special investigations are aortography and divided renal-function studies. Peart and colleagues emphasize that aortography alone may sometimes be misleading, owing in some cases to streaming of the radio-opaque medium, with consequent apparent narrowing of the artery. They emphasize that the two tests should be regarded as complementary and suggest that divided renal-function studies are essential for establishing the diagnosis of renal-artery stenosis. The significant findings from ureteric catheterization are a diminished volume of urine and diminished clearance of sodium *para*-amino-hippurate (P.A.H.) and creatinine from the side of the affected kidney, owing to the smaller volume of glomerular filtrate. In addition the urinary concentration of inulin and P.A.H. is increased, while that of sodium and potassium is decreased. Since the kidney treats the radio-opaque dye used for intravenous pyelography in the same manner as P.A.H., greater concentration of dye will result on the affected side and hence the affected kidney may, paradoxically, show more clearly in the intravenous pyelogram. This important point needs emphasis lest the investigator go astray.

The ideal operation for this condition is reconstruction of the arterial supply to the kidney rather than nephrectomy, because the kidney on the affected side may be the better of the two after restoration of a normal arterial supply. It is uncertain, however, how far the varying amounts of tubular, and to a lesser extent glomerular, damage are reversible after operation. The techniques of reconstruction include thrombendarterectomy, spleno-renal anastomosis, renal-artery reimplantation into the aorta, excision of the stricture, and a bypass graft, selected in each case according to the type of stenosis present. Only occasionally is nephrectomy advisable. The results of operation in carefully selected cases seem to be good. So an awareness of the possibility of renal-artery stenosis as a treatable cause of hypertension may in future lead to its recognition in patients in whom this lesion would previously have remained undiagnosed.

VACCINATION AGAINST MEASLES

J. F. Enders and his colleagues[1] have shown that the Edmonston strain of measles virus can be attenuated by a series of passages through tissue cultures of human kidney, human amnion, chick embryo, and embryonated eggs. The attenuated strain produced no disease when inoculated into monkeys, and only mild disease in susceptible children, with subsequent development of measles antibodies.[2]

Recently, A. J. F. Schwarz and his colleagues[3] have prepared an experimental live measles vaccine by growing the attenuated Edmonston strain in chick-embryo tissue culture. The vaccine was lyophilized and stored refrigerated. Cynomolgus monkeys inoculated with this vaccine by the oral, intramuscular, or intracerebral routes showed no signs of disease, but they all developed measles-neutralizing and complement-fixing antibodies. Two children aged 2½ years and 4 years, with no demonstrable measles antibody, were inoculated with 1.0 ml. of the vaccine intramuscularly. In both children a fever was noticed about a week after inoculation, but no rash or Koplik spots were observed and they both developed measles-neutralizing and complement-fixing antibodies.

During a measles epidemic in Panama in the spring of 1959[4] a batch of this measles vaccine was tested on 453 persons with no history of clinical measles. Children under 5 years of age received 0.5 ml. of the vaccine intramuscularly, and subjects aged 5–30 received 1.0 ml. by the same route; 356 others served as controls. In a 4½-month period after vaccination only 0.7% of the vaccinated subjects developed measles, whereas measles occurred in 9% of the non-vaccinated control group. However, 80% of the children under 5 years of age who received the vaccine developed some fever a week later, 50% developed a rash, and nine required hospital treatment. There were no apparent reactions to the vaccine in the older children or in the adults. It seems likely, therefore, that further attenuation of the measles virus will be required before it can be used for vaccinating young children.

An obvious alternative is to prepare a formalin-killed vaccine, but unfortunately the titres which can be obtained in chick-embryo tissue cultures are too low to make this practicable. The attenuated Edmonston strain grown on Girardi's human heart tissue cells[5] can attain titres which might be sufficient for a killed vaccine, but at present it is impossible, because of the neoplastic appearance of adapted cell lines, to advocate their use for vaccine production.

Another possibility being examined is to exploit the antigenic similarity (but not identity) of measles and distemper viruses.[6] An egg-adapted strain of distemper virus[7] was grown on chick-embryo tissue culture,[3] and the vaccine prepared from it was lyophilized and stored refrigerated. This distemper vaccine was given intramuscularly to 388 persons during the measles epidemic in Panama[4]; 414 others served as controls. The vaccine caused no reactions or signs of illness, but significant protection against measles was found only in young children under 6 years of age, the reduction of cases in this group being about threefold. If a distemper vaccine is to be used, certainly for older children and adults, a strain with a closer antigenic relationship to the measles virus will have to be found. Probably it will be easier to isolate an avirulent variant of the measles virus which will give effective and safe protection for all age groups.

THE E.O.G.

Electro-oculography is a method of measuring eye movement which is fast gaining popularity. Though the use of the E.O.G. is recent, the basic phenomenon was discovered so long ago as 1842, when Du Bois-Reymond[1] described the steady current that flows from fundus to cornea across the living eye. This observation attracted much less attention than the later finding[2] that, when the eye was exposed to light, rapid changes in the resting current could be observed. These rapid changes of current reflect the activity of the nervous part of the retina, and recordings of them ("electroretinograms") have been used both experimentally and clinically as a convenient objective test of retinal function. When making electroretinograms it is convenient to block off the constant resting current, which is disregarded.

However, the generators of the resting current have a singular property, which forms the basis of a new method of electro-oculography. They appear to be orientated in the visual axis, and the current they produce flows symmetrically through the tissues which surround the eye. Therefore, as the eye moves, the current field round it moves also, in much the same way as the field of a magnet moves if the magnet is turned. Small wire electrodes placed on the skin near the eye will record the changes in the current field, and hence any eye movement.[3]

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Other methods of recording eye movements require the subjects to be fixed to complex apparatus. In contrast, electro-oculography is easily carried out and suitable for clinical use. The electric potentials recorded are linearly related to the angular deviation of the eyes, and though recent papers have described more sophisticated techniques, designed to explore the full sensitivity of the method,[4] any electroencephalographic apparatus can be easily modified so that it will record all but the smallest eye movements. Much work has been done on the recording of nystagmus.[5 6] The amplitude and rate of nystagmoid movements can be accurately measured in relation to the direction of gaze, and the end-point of caloric or rotational nystagmus determined with great accuracy. Many other uses have been reported—for example, in aviation medicine—and in the analysis of reading in children's clinics defects can be detected and analysed.[7] Pareses of extraocular muscles in midbrain lesions can be analysed, and the progress followed more accurately than by clinical observations.[8] Distinctive patterns of eye movements have been described which serve to distinguish amblyopia from lesions of the optic pathway.[9]

The site of origin of the E.O.G. has attracted little attention. It is generally assumed to be produced by some retinal structure, though both the lens and cornea are electrically charged. However, it has recently been shown that the size of the E.O.G. varies rhythmically, has diurnal variation,[10] and is affected by acapnia, anoxia, and the administration of adrenaline. In addition, changes of illumination alter the magnitude of the E.O.G.,[11 12] and it is suggested that the potential is "metabolic" in origin. If this is so, then the E.O.G., apart from providing an index of eye movements, may also provide a method of investigating the metabolism of the retina, and it is interesting that abnormalities in the E.O.G. have been reported in a case of retinal degeneration[13] in which there was no question of abnormal eye movements. It is even perhaps possible that changes in the metabolism of the central nervous system (of which the retina is a part) may be studied by this new technique.

AGE OF THE MENARCHE

There are broadly two ways in which the age of the menarche can be investigated in large populations: by asking women when menstruation began, and by asking girls whether it has begun. The second is the more reliable method, but the first has been the source of most recorded data and is probably responsible for some of the inaccurate reports in the literature.

For example, it was once thought that women mature earlier in hot than in temperate or cold climates. Recent observations suggest that any difference which exists is small and usually in the opposite direction. R. W. B. Ellis[1] showed that the mean age of the menarche was slightly higher in Nigerian girls (14.2 years) than in British nurses (13.7), in spite of exposure to vastly different environmental conditions. D. C. Wilson and I. Sutherland[2] found no consistent difference in age of maturation of girls in England and in tropical countries such as Nigeria, Ceylon, and India. And a recent estimate of the age of the menarche (13.4) for Indian women[3] is remarkably close to figures fairly consistently recorded in the Western world—for example, 13.7 in Copenhagen[4] and 13.6 in Yugoslavia.[5] The observed geographical variation clearly would not justify the conclusion that the age of the menarche is much affected by environmental influences such as climate and economic and social circumstances, or even by inherited differences associated with race.

The only impressive evidence of environmental influence is the striking secular trend in the age of the menarche. It is said to have been about 17.0 in the mid-nineteenth century, and appears to have declined at the rate of approximately four months per decade.[6] There must of course be reservations in accepting conclusions based on nineteeth-century estimates, but similar results have been obtained independently in a number of countries. Moreover, the trend towards earlier sexual maturity has not yet been arrested. Wilson and Sutherland[7] found that the mean age of the menarche was 13.38 years in Dorset day schools in 1949 and 13.03 years in Sussex day schools in 1957. This result might be attributable to a difference between the two areas, but since geographical variation is small it seems more probable that it reflects the consistent secular trend in the age of the menarche.

The reasons for this trend are by no means clear. It has been suggested that it may be due to improvements in diet, an explanation consistent with the retardation of sexual maturity in countries where nutrition was seriously deficient during the war.[8] If inadequate diet was the main influence, however, it might be expected to have a more conspicuous effect on the age of the menarche in countries such as India and Africa.

P.R.C.O.G.

Mr. Arthur C. H. Bell, F.R.C.S., F.R.C.O.G., was elected President of the Royal College of Obstetricians and Gynaecologists at a meeting of its council on July 23 in succession to Sir Andrew Claye. Mr. Bell has had a distinguished career in his chosen specialty since qualifying at St. Bartholomew's Hospital in 1927. He is a nephew of the late Professor William Blair-Bell, one of the founding fathers of the College and its first President.

NEW EXTENSION TO B.M.A. HOUSE

Lord Nuffield on July 21 opened the new wing of B.M.A. House known as Tavistock House East. An account of the ceremony appears in this week's *Supplement*, with photographs of the interior of the building described and illustrated in the *Supplement* of last week.

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Drug Treatment of Disease

DRUG TREATMENT OF TUBERCULOSIS

I. STANDARD CHEMOTHERAPY

BY

JOHN CROFTON, M.D., F.R.C.P., F.R.C.P.Ed.

University of Edinburgh

The aims of the drug treatment of tuberculosis are to arrest the patient's disease, to render him uninfectious, and to prevent relapse. In patients with pulmonary tuberculosis whose organisms are initially sensitive to the standard drugs it should be possible to achieve these aims in all, or virtually all, patients provided the drugs are carefully prescribed and carefully taken. Error on the part of either doctor or patient can lead to the emergence of drug-resistant organisms. The patient with such organisms may be extremely difficult to salvage. In few other conditions can apparently minor error lead to such ultimate disaster for the patient.

Standard Drugs

The three standard drugs in the treatment of tuberculosis are streptomycin, isoniazid, and the salts of para-aminosalicylic acid (P.A.S.). A number of other drugs are now available, but none of them has yet found a place in the routine treatment of patients. They are at present reserved for those whose organisms are resistant to the standard drugs.

Toxic Effects of the Standard Drugs

Streptomycin

Streptomycin is available as the sulphate or as the calcium chloride complex. The drug is given by intramuscular injection, and the sulphate is the least painful salt. The two main toxic effects are *vestibular upset,* resulting in giddiness, and hypersensitivity reactions. Vestibular upset, if it occurs at all, usually does so within the first three months of administration; the liability to giddiness does not seem to increase with prolonged administration beyond this period. Vestibular damage appears to be more common in older people. Even a relatively slight renal insufficiency is liable to result in the retention of streptomycin, with consequent risk of vestibular damage. If there is any likelihood of renal impairment, it is wise to investigate the serum levels of streptomycin.

Our standard practice is to give 1 g. streptomycin intramuscularly and to estimate the serum level 24 hours later. If the level is greater than 1 μg. per ml., there is retention of streptomycin, and the dose should be lowered accordingly. If giddiness does occur streptomycin should be immediately stopped. It is normally possible to continue chemotherapy with P.A.S. and isoniazid. If streptomycin is stopped as soon as giddiness begins, recovery is usual, but if the drug is continued after the vestibular damage has occurred recovery may take many months, especially in older people.

Deafness due to streptomycin is extremely rare if the drug is given in normal doses by the intramuscular route. It may occur after intrathecal streptomycin. A modification of streptomycin, dihydrostreptomycin, was introduced in an endeavour to reduce the incidence of vestibular damage. Vestibular damage is certainly less common with dihydrostreptomycin but unfortunately this drug may cause deafness even when given by the intramuscular route. It should never be given intrathecally.

It has been suggested that the incidence both of vestibular damage and of deafness may be reduced by using a mixture of dihydrostreptomycin and streptomycin, but the incidence of auditory damage seems to be sufficient for this combination not to be recommended for routine use.

Hypersensitivity reactions are relatively frequent with streptomycin. They usually come on within the first four weeks of treatment and are manifested by fever or rash or both. Occasionally there may be enlargement of the lymph glands as well. Any fever occurring within the first month of treatment should be regarded as due to drug hypersensitivity until proved otherwise. The drug should be immediately stopped until the reaction has subsided. P.A.S. and isoniazid will have been stopped at the same time, for hypersensitivity may be due to P.A.S. also.

A test dose of streptomycin is then given. If the reaction has not been a severe one, it is reasonable to give a dose of 0.5 g. If the reaction has been severe then it is wise to start with a smaller dose, perhaps 0.1 g. If the patient is hypersensitive, a rash or some rise in temperature usually occurs within a few hours. If there is no response a larger dose can be given. If there is no reaction to a full dose the patient is not hypersensitive to streptomycin.

If hypersensitivity is proved, it is usually adequate to start desensitization with a dose of 0.1 g., though lower initial doses may have to be given to some patients who have had very severe reactions. The dose can normally be increased at the rate of 0.1 g. daily. If there is any reaction it is well to repeat the previous dose after the reaction has subsided and then to work the dose up slowly again. Desensitization is normally possible within two to three weeks. In occasional patients who are very hypersensitive, desensitization may have to be carried out under cover of corticosteroid drugs.

Isoniazid

In the doses recommended below for treatment of all tuberculosis except tuberculous meningitis, isoniazid only very rarely indeed gives rise to any side-effects. The most common side-effect is peripheral neuritis, usually manifested by a burning sensation in the limbs. Psychotic upsets have also been described. When very large doses of isoniazid are given, such side-effects are a definite hazard, and their incidence is said to be greatly reduced by giving prophylactic pyridoxine at the same time as the isoniazid. A daily dose of 60 mg. seems to be adequate for this purpose. Hypersensitivity reactions to isoniazid are very rare and usually occur in patients who are also sensitive to streptomycin and P.A.S. Desensitization can proceed on similar principles.

P.A.S.

In Great Britain P.A.S. is normally given orally. The most important side-effects are *nausea* and *diarrhoea*. Nausea is relatively common when the higher doses, such as 20 g. of the sodium salt daily, are given, but is very much less usual when P.A.S. is given in a daily dose of 10 g. It often helps to take the dose in the middle of a meal. In severe cases it may be justifiable to reduce the dose somewhat and then work it up gradually. Several preparations are on the market which are alleged to improve the tolerability of P.A.S., but some of these are not well absorbed from the gut. We have found two preparations—"bactylan," and P.A.S. and isoniazid tablets (Carnegie)—to improve tolerance and to be well absorbed.

Diarrhoea is less common but may be very troublesome. It is usually not prevented by using enteric-coated preparations. If small doses of tinct. opii are given, this will often allow the bowel to become accustomed to the drug, and the tinct. opii can be withdrawn after quite a short time. Very occasionally a patient is quite unable to tolerate P.A.S.

Hypersensitivity reactions are common and their manifestations are similar to those of streptomycin, though jaundice and even encephalitis have been described in severe cases. The principles of desensitization are also similar. If the reaction has been mild a test dose of 2.5 g. is adequate, but with a more severe reaction a lower test dose, such as 0.5 g. or even 0.1 g., may be necessary. When desensitizing in the ordinary case, an initial dose of 0.5 g. is usually small enough, though after a very severe reaction the initial dose sometimes has to be very much smaller. In the usual case a daily increment of 0.5 g. is adequate, and desensitization is completed in two to three weeks.

Simultaneous hypersensitivity to streptomycin and P.A.S. is not uncommon, and tests should always be carried out to both drugs. It is probably best to begin by desensitizing to P.A.S., to which resistance is less readily acquired, and to add in isoniazid when the patient is able to tolerate half the normal daily dose of P.A.S. When the full dose of P.A.S. has been reached P.A.S. and isoniazid can be continued while desensitization to streptomycin is proceeding.

P.A.S. has a weak *anti-thyroid* action. Some patients who have been on it for six months or more may develop a goitre or even hypothyroidism. Either can be relieved, while continuing the P.A.S., by administering thyroid. Thyroid function returns to normal when the patient ceases to take P.A.S.

Drug-Resistance

Tubercle bacilli readily acquire resistance to all three of the standard drugs. A proportion of naturally resistant mutants occurs in any large population of bacilli. Under the influence of a single drug the resistant bacilli gradually increase until the sensitive population are replaced by the descendants of the resistant mutants. Fortunately by giving proper doses and combinations of drugs the emergence of resistant tubercle bacilli can be avoided in all, or almost all, cases. The mutants naturally resistant to one drug are eliminated by the other. If the patient's tubercle bacilli have become drug-resistant, they usually remain so permanently. With single drug therapy in a patient with a large population of tubercle bacilli, resistant organisms may occur as early as two or three weeks after starting treatment, though more commonly in four to eight weeks.

When a patient's bacilli becomes resistant to a drug, then that drug ceases to be effective. In particular, if given in combination with a second drug, it fails to prevent the emergence of bacilli resistant to the second drug. The criteria for drug resistance vary considerably in different centres. Experience in this department has shown that the lowest detectable degree of drug resistance may be clinically significant.

Unfortunately a patient who develops drug-resistant organisms may pass these on to others, and a previously untreated patient may present with organisms which already are resistant. Surveys have shown that between 5 and 7% of newly diagnosed patients have organisms "primarily" resistant to one or more of the standard drugs. Fortunately only a very small proportion of patients have organisms primarily resistant to two standard drugs.

If proper chemotherapeutic combinations are widely used, resistant organisms should not develop and should not be diffused in the community. The incidence of primary drug-resistance should therefore diminish. But at the present time, in certain parts of the world at least, the incidence is probably rising.

Recommended Drug Combinations

The following drug combinations are based on carefully controlled comparative studies of the Medical Research Council. Most have been used for seven to eight years by the Edinburgh group, with, in pulmonary tuberculosis, almost uniform success in converting the sputum to negative, provided the organisms were initially sensitive to at least two of the standard drugs.

(1) Hospital Patients Under Age 40

Streptomycin 1 g. daily intramuscularly +sodium P.A.S. 5 g. three times daily +isoniazid 100 mg. twice daily.

All three drugs are given initially in case the patient has been infected with organisms resistant to one of the drugs. The remaining two drugs would then form an effective combination in preventing resistance. The dose of 100 mg. isoniazid twice daily was used in the Medical Research Council trial but is lower than the dose used in very many parts of the world. It has been found that many patients metabolize isoniazid rapidly, and it has been suggested that the dose of the drug should be based on serum estimations. But at least in British conditions this seems unnecessary, for even with our lower dose several series have been published showing uniform conversion of the sputum to negative and without the emergence of resistant bacilli.

(2) Hospital Patients Over Age 40

Streptomycin 1 g. three times weekly +sodium P.A.S. 5 g. three times daily +isoniazid 100 mg. twice a day.

The lower dose of streptomycin in this group is given because of the risk of vestibular disturbance in older people. Theoretically there might be a slight risk of drug resistance with this combination, for if the patient's organisms were primarily resistant either to P.A.S. or to isoniazid he would virtually be receiving intermittent streptomycin with daily doses of the other drug. In practice we have not seen a failure of this type, but it

remains a theoretical possibility. Perhaps it might be safer to give a daily dose of 0.5 g. streptomycin, but we have at present no evidence that this would be superior.

In the case of hospital patients under the age of 40, once it is known that the pre-treatment cultures were sensitive to all three drugs the P.A.S. may be stopped. The combination of daily streptomycin and isoniazid has been shown in the Medical Research Council trials to be the most efficacious. In patients over the age of 40 we cannot stop the P.A.S., as it is risky to give intermittent streptomycin with daily isoniazid: some patients may develop isoniazid-resistant organisms.

(3) Mild Cases Treated as Out-patients and Patients After Discharge from Hospital

It is convenient to treat the patients in these categories with oral drugs. The usual combination is 5 g. sodium P.A.S. together with 100 mg. isoniazid, both twice daily. Isoniazid and P.A.S. are given in the same cachets or the same tablets, so that the patient cannot take one without the other.

In newly diagnosed patients with mild disease there is the theoretical objection that some of these patients may have been infected with organisms resistant to one of the drugs, with the risk of the development of resistance to the second. It might be safer to administer all three drugs, at least until it is known that the pre-treatment cultures are sensitive or negative. But there may be an even larger hazard if the patient is given his streptomycin injections and fails to take his P.A.S. and isoniazid. It is possibly therefore a lesser risk to prescribe P.A.S. and isoniazid from the beginning of treatment and to keep streptomycin in reserve.

Risky Chemotherapy

Certain drug combinations and commercial preparations of drugs, though they may be successful in the majority of cases, may give rise to a much higher failure rate than the standard drug combinations mentioned above. The Medical Research Council trials showed that streptomycin given twice a week with daily isoniazid resulted in isoniazid-resistant organisms in up to 13% of patients within six months. When streptomycin was given daily with P.A.S., a daily dosage of 5 or 10 g. P.A.S. was greatly inferior, in preventing streptomycin resistance, to a daily dose of 20 g. Our experience has suggested that intermittent streptomycin with daily P.A.S. also carries a risk of the emergence of drug resistance.

Several preparations are on the market which consist of chemical combinations between P.A.S. and isoniazid, mixtures of isoniazid with thiosemicarbazones or other drugs, or allegedly better tolerated forms of P.A.S. It is probable that most of these preparations are less effective than the standard combinations. It is unwise to use any of them until they have been tested out in a really critical and scientific manner. The unsupported assurances of advertising material should not be accepted.

Duration of Chemotherapy

Studies of the relation of relapse rate to duration of chemotherapy, and also studies of the isolation of tubercle bacilli from lung lesions resected after varying periods of chemotherapy, suggest that one year should be the minimum period of chemotherapy in any form of tuberculosis, however mild. In moderately severe cases chemotherapy should be continued for eighteen months; in very severe cases, including those with residual open cavities, for two years. There is little present evidence that a duration of more than two years is necessary. Among 260 cases of pulmonary tuberculosis admitted to Edinburgh hospitals with sensitive organisms in 1953 and 1954, and receiving a minimum of eighteen months' chemotherapy, there were no relapses within three to five years.

Corticosteroid Drugs

It has been established that corticosteroid drugs given in severe pulmonary tuberculosis increase the rate of subjective improvement, weight gain, and radiological clearing, at least during the early months of treatment. Nevertheless, at least when prednisolone in a daily dosage of 20 mg. was given for three months, the ultimate results in the patients who received corticosteroids were not significantly better than in the controls.

It is of course highly dangerous to give corticosteroid drugs if the patient's organisms may not be sensitive to the chemotherapy in use. There seems little point in using corticosteroid drugs as a routine. The risks are not balanced by any ultimate benefit to the patient. But corticosteroids may keep alive a patient who is admitted moribund until the antituberculous drugs can take effect. In patients who are very toxic, corticosteroid drugs may be given in the earlier weeks, largely for humanitarian reasons. As already mentioned, they also have a place in the treatment of patients with severe hypersensitivity reactions in whom desensitization may prove difficult.

Failure of Out-patients to Take Drugs as Prescribed

When it became possible to test for P.A.S. in the urine it soon became obvious that many out-patients failed to take their drugs as prescribed. The physician must be tireless in persuading the patient to take his drugs regularly. It is important that the possible disasters which may result should be explained not only to the patient but also to his near relatives. For, even when P.A.S. and isoniazid are made up in the same cachet, if the patient fails to take the appropriate number of cachets during the day his bacilli can become isoniazid-resistant.

For patients judged to be unreliable it may be possible to arrange a daily injection of streptomycin, with simultaneous administration of the full daily dose of isoniazid under the nurse's supervision.

Chemotherapy of Non-Pulmonary Tuberculosis

The principles of the chemotherapy of non-pulmonary tuberculosis are very similar to those already outlined. In the case of tuberculous meningitis many clinicians give a daily dose of isoniazid of 10 mg. per kg. body weight in two or more divided doses. It is uncertain whether intrathecal streptomycin is necessary. In any case a daily intrathecal dose should not exceed 100 mg. streptomycin and in young children 50 mg.

Intrathecal isoniazid has been advocated and is possibly justified in very severe cases. The intrathecal dose should not exceed 40 to 50 mg. daily for an adult and correspondingly smaller doses for children. Pure isoniazid powder must be used and the solution sterilized by filtration.

Tuberculosis of the urogenital tract responds excellently to chemotherapy, and arrest of the disease

should be as well assured as in pulmonary tuberculosis. However, healing may give rise to scarring and stenosis and this in turn may lead to mechanical difficulties. In all cases of renal tuberculosis, streptomycin levels in the serum should be estimated early in treatment in case there is retention of the drug. In all severe forms of extrapulmonary tuberculosis it is wise to continue chemotherapy for at least eighteen months.

Conclusions

Provided proper sensitivity tests have shown that the patient's organisms are sensitive to the standard drugs and that chemotherapy is scrupulously prescribed and scrupulously taken, it should be possible to arrest the disease permanently in the vast majority of cases. There may be very occasional failures in patients admitted moribund, in cases of severe tuberculous meningitis, or in miliary tuberculosis in young infants. But any carelessness by the doctor in prescribing, or by the patient in taking, his drugs are liable to result in ultimate drug resistance and often in subsequent disaster for the patient. Unfortunately such carelessness is still all too common. Treatment of its results will be discussed in the next article in this series.

ADDER-BITES IN CORNWALL

BY

T. C. MORTON, C.B., M.D., F.R.C.P.

Air Vice-Marshal, R.A.F. (Ret.); Pathologist, West Cornwall Clinical Area

In the last eight years I have seen 12 cases of adder-bites in adults and children and have been consulted about another six. In 14 years in the Middle and Far East I have treated only two cases of snake-bite in Europeans. What is the reason for this anomaly?

During the holiday season, from mid-June until mid-September, Cornwall is faced with an influx of visitors, mainly from the industrial north. The majority are town-bred people, complete strangers to our countryside, in holiday mood, and intensely curious and interested in their unfamiliar environment of tent, caravan, or bed-and-breakfast with its compulsory accompaniment of alfresco meals by lane, wood, or beach.

This period coincides with the breeding season of *Vipera berus*, our only venomous snake. Nearly all the bites I have been consulted about have occurred on the fingers or arms due to foolish attempts to capture or handle the vipers.

The Criminal

The adder (*Vipera berus*) is not an aggressive snake, it strikes only in self-defence when handled or trodden on; where the human race is concerned it is never the aggressor. It is a short stumpy snake; the largest recorded British specimen was 2 ft. 3 in. (68.5 cm.) in length—this was a female; the male is 2 to 3 in. (5 to 7.5 cm.) shorter. It is usually possible to distinguish the sexes by the coloration: whitish or pale-grey specimens with a black belly and jet-black dorsal markings are males; brown and brick-red specimens with the markings of a darker brown or red are females. The markings vary considerably; those on the back usually consist of a wavy or zigzag longitudinal band; rarely, the markings may be absent altogether and occasional black melanistic specimens occur (Boulenger, 1913).

Vipera berus is the only poisonous snake in Great Britain; it is absent in Ireland. As in all vipers, the two poison fangs are hollow and are present in the posterior extremity of the erectile maxilla; the venom from the poison gland (a modified salivary gland) is injected into its prey to immobilize it and facilitate swallowing and also digestion. The venom of *Vipera berus* is not very toxic; the minimum lethal dose (M.L.D.) for a 600-g. guinea-pig is 40 mg., as compared with the M.L.D. of a Russell viper which is 1 mg. for a similar-sized guinea-pig. The venom contains a small amount of neurotoxin, which varies considerably in the different species of the same genus. Haemorrhagins are also present. The haemorrhagin has a special affinity for the endothelial cells of the finer capillaries, causing lysis of the cells and subsequent haemorrhagic oedema or small petechiae. The latter may be present at the site of the bite and may spread up the affected limb. Oozing of blood from the site of the bite occurred in only one of our Cornish cases; no sloughing of tissues occurred, so the cytotoxins present in the venom, although responsible for the oedema and swelling, are not very toxic.

Feeding Habits

The food of the adder is very varied; baby rabbits, weasels, mice, voles, shrews, moles, birds, lizards, slow-worms, frogs, and large slugs have been found in the stomach. It swallows its prey whole, the neurotoxin paralysing it and the cytotoxins and haemorrhagins injected deeply into the victim facilitating digestion.

Hibernation occurs during the colder months of the year, but bites have been recorded from March until October.

I am convinced that the varying severity of adder-bites in this country is dependent on whether the snake has bitten anything recently. This is well exemplified in the case of a boy aged 11, who was bitten on the left index finger and then on the right index finger. No haemorrhagic bullae developed on the right index finger, and the purpuric petechiae and swelling of the right hand and arm were much less. Similarly, the only adult male whose condition gave rise to anxiety was bitten in the early spring by a hibernating viper.

Reproduction

Pairing takes place in April and May, and the young, 5 to 20 in number, are born in August and September. The young, on releasing themselves from the transparent membrane in which they are enclosed at birth, measure 6 to 8 in. (15 to 20 cm.) in length and feed on insects and worms.

Natural Enemies

Owing to the dearth of rabbits since the onset of myxomatosis the buzzards in Cornwall have been seen killing adders by flying upwards with the adder in their talons and dropping it from a height of about 150 ft. (46 m.). The water bailiff at the reservoir assures me that he has seen this on at least three occasions. The stunned snake is then torn to pieces and eaten by the buzzard.

Mortality Rate from Adder-bites in the U.K.

Walker (1945), in his summary of the accounts of 50 cases reported to him, states that there had been seven deaths from adder-bite in England and Wales up to the year 1945. He was able to trace five of these fatal cases. The particulars of these are as follows:

No.	Sex	Age (Years)	Previous Health	Duration (Hours)	Mode of Death
1	M	11	Delicate	12	Collapse: cardio-respiratory failure; conscious
2	M	4½	Healthy	60	Circulatory collapse; unconscious
3	F	3	,,	6	,, ,,
4	F	6	Delicate	36	,, ,,
5	M	51	Insane. W.R. +	26	Unconscious, with T. 102° F (38·9° C.), bounding pulse and stertorous breathing

The Registrar-General for Scotland informs me that no deaths from viper-bites occurred in Scotland during 1950–8. The Registrar-General for England and Wales informs me that the most recent deaths assigned to snake-bite occurred in two males in 1941.

In 1957 a boy of 14 collapsed and died a few minutes after he had been given antivenin serum as treatment for an adder-bite. Death was attributed to cardio-vascular collapse from anaphylaxis due to the serum (*Lancet*, 1957).

We are faced with the anomaly that so far as England and Wales is concerned the only death reported from adder-bite for the last 18 years was due to anaphylaxis from the antivenin given. On the other hand, the deaths due to adder-bite collected by Walker had received no antivenin and at that time no anti-histamine preparations were available. It is therefore probable that the present reduction in the mortality rate is due to the more general use of antihistamine drugs and antivenin. Dr. S. Campbell, of St. Just, who has treated numerous cases of adder-bite, relies on "piriton" and rarely finds it necessary to give anti-venin.

A feasible explanation for a death occurring in an adult is the fortuitous puncture of a vein by the poison fang—quite a likely event in a middle-aged person with extensive varicosities about the ankle.

The Victim

The ages of those bitten varied from 5 to 45 years. There were no fatalities, and in only four cases were there marked general symptoms in which hospital treatment was imperative. All the bites were on the extremities—nine the hand and three the ankle.

Sir Philip Manson-Bahr (1957) states that the venom of the adder in this country is of low toxicity. It rarely, if ever, kills adult humans and is dangerous only to small children. He wisely points out that the main danger to life arises much more from the heroic and often obsolete methods of treatment so often applied than from the viper venom itself.

Up to the year 1957 I could not have agreed more with this expert opinion, but in 1958 I encountered three cases of adder-bite of unusual severity which proved how effective intramuscular or subcutaneous specific anti-viper serum can be. The serum available is the Pasteur Institute E.R. serum in ampoules of 10 ml. for neutralizing the venom of vipers in France (*Vipera berus* and *Vipera aspis*). There they recommend subcutaneous injection locally if possible and warn one against anaphylactic reactions, especially in subjects allergic to horse serum. Serum-sickness occurs in a large proportion of cases, usually about the seventh to tenth day. Analysis of the antivenin shows specific gravity, 1028; total proteins, 7.2 g./100 ml. (albumin 0.8 g., globulin 6.4 g.).

The results of an adder-bite are completely unpredictable, as they depend on the amount of venin injected and the age and constitution of the patient. The effects are local and general; the former are constant but variable in intensity, the latter may be negligible in adults.

Local Reaction

A sharp pain is felt at the time of the bite, which an intelligent girl described to me as being like a jab with a red-hot needle. This is followed by oedema, eventually showing haemorrhagic discoloration and spreading usually up to the groin or axilla in the case of the limbs. It reaches its maximum intensity in from 6 to 24 hours. In addition, petechiae may develop in the vicinity of the bite and occasionally spread up the lymphatics, and the adjacent lymph nodes may become swollen and tender. Occasionally, in a bite on the finger or toe, haemorrhagic blisters develop in 48 hours; this occurred only once in our series. In a girl of 17 who was bitten on the wrist the whole arm and shoulder became very oedematous and went completely canary yellow within 14 hours. A similar reaction was reported by Goddard (1951) in an adult male.

General Reaction

Reactions vary greatly in intensity from mild to profound collapse. Giddiness associated with sweating may develop some 20 minutes after the bite. This may pass off in mild cases, but in many others persistent and severe vomiting occurs, together with marked cardio-vascular collapse which may go on to drowsiness and semi-consciousness, especially in young children. These general symptoms usually develop within the hour, and our experience has been that if they have not developed by the end of two hours after the bite the case will be mild and no antivenin is necessary. It is usually at least two hours before patients arrive at the Royal Cornwall Infirmary, so that it is easy to decide if anti-venin is really required or if antihistamines, rest, and reassurance are all that are necessary; at times it is difficult to convince relatives and practitioners that this is sound advice.

The earlier the onset of general symptoms the greater the shock and vomiting and the local reaction to the bite. Our patients recovered completely from their general symptoms in from 2 to 12 hours after admission to hospital, but the oedema persisted in one case for over four weeks and was associated with discomfort on walking for much longer; eventually a complete recovery was made with no residual after-effects. Curiously enough, this was the only case which received immediate local treatment. The patient was bitten on her ankle while walking near the Lizard. A passer-by applied a tight bandage above the bite and within 20 minutes she was given antivenin locally around the bite. The local practitioner who treated her always keeps antivenin in his refrigerator, as he has seen several adders in his garden and is naturally apprehensive about his young children. (Pasteur Institute E.R. serum was given.)

Circumstances Under Which the Victims Were Bitten

These circumstances varied from the ridiculous to the bizarre.

A party of young children found a hibernating adder in March. They sat in a circle prodding it with twigs until the snake awoke from its torpor and bit the main aggressor, aged 5, on the hand.

A man on holiday from the Midlands chased and captured an adder by the tail. On being asked why he did this he said he wanted to crack its head off like cracking a whip. On inquiring why he wanted to do this he replied that he had seen a cowboy do this in a strip cartoon. He was bitten on the thumb and was admitted slightly shocked and sweating; his hand and thumb were considerably swollen. He was given 10 ml. of serum subcutaneously and detained for the night. Apart from slight residual swelling he was none the worse for his cowboy exploit, of which he was more proud than ashamed.

There were only four instances out of the 16 bites in which the victim was not to blame.

A naval airman was climbing the cliffs near Mullion and, in reaching for a hand grip above his head, inadvertently placed his hand on a viper which was lying torpid in the sun. It says much for the stoicism of the Senior Service that he did not relinquish his hold and fall backwards over the cliff. He was bitten on the dorsal surface of the middle phalanx of his right thumb. His general condition was excellent, and as he gave a very bad history of asthma and hay-fever no antivenin was given. The thumb was grossly swollen to about three times its normal size compared with the left thumb, and two fang marks were clearly visible. No local or general treatment was given, and he never vomited or showed any signs of shock. His hand was still swollen to a less extent next day, but no petechiae developed and he returned to his unit at his own request. This was the mildest case of adder-bite encountered.

Two Severe Cases

A sea scout aged 11, in camp near the Lizard, stated that his scoutmaster picked up a snake by the neck and demonstrated it to the boys as a harmless grass snake; he then put it down on the ground and the boy picked it up with both hands and was bitten first on the index finger of his left hand and then on the index finger of his right hand. He promptly threw the snake away. He was admitted two hours later very shocked and vomiting bile-stained fluid. The middle phalanx of the left index finger showed two fang punctures and was tense and very swollen; the middle phalanx of the right index finger showed two similar fang marks but was only slightly swollen. He was given 10 ml. of antivenin intramuscularly into each buttock and vomiting ceased an hour later. Considerable swelling of both arms followed and two large haemorrhagic bullae appeared on his left index finger 48 hours later, together with some small purpuric patches on the dorsum of the hand. His general condition was excellent after 15 hours, but gross swelling of both arms persisted for four days and necessitated his being fed. It was possible to discharge him back to his camp at the end of 10 days. He later had to be readmitted to a small local hospital with marked serum sickness in spite of having been on a prophylactic dose of promethazine all the time he was in hospital.

A girl of 17 on holiday, living in a caravan near a wood, sat down and felt a sharp prick on her left arm, and on looking down saw two drops of blood on her left wrist but saw no snake, wasp, or hornet. The undergrowth where she was sitting was a tangled mass of vegetation. She returned to her caravan and called to her neighbour, as she began to feel very nauseated. She was brought to the hospital in a state of collapse and vomiting bile-stained fluid, and was grossly confused mentally. She was given glucose-saline intravenously, but no local treatment was attempted, as the casualty officer thought it was an allergic reaction to a wasp-sting and she was too collapsed to give a history. Her left arm was grossly swollen to the elbow, and, on being asked to see her, I decided to give her 20 ml. of antivenin; she then slowly recovered from her shock. The next morning the left arm was swollen from the hand to the shoulder and was a bright canary yellow in colour; her general condition was excellent. On examining the arm at the end of four days, when the gross swelling was beginning to subside, two puncture marks 1 cm. apart could be made out. She was treated with promethazine hydrochloride 24 mg. t.i.d., and her condition gave no further cause for anxiety. Liver-function tests on August 26 were perfectly normal. A blood count on August 22 showed: clotting-time, 1 minute 30 seconds; bleeding-time, 1 minute 48 seconds; haemoglobin, 113%; red blood cells, 5,200,000/c.mm.; total white count, 11,600/c.mm. (polymorphonuclears 81%, lymphocytes 17%, monocytes 2%). Her arm was still very swollen and canary yellow on discharge on August 28. Her general practitioner informed me that her arm was still swollen and yellow on September 1. She continued taking promethazine until September 8, by which time the swelling had almost subsided and no serum sickness or urticarial rash had developed.

Discussion

"There are nine-and-sixty ways of constructing tribal lays. And every single one of them is right," says Kipling. Alas, this does not apply to the treatment of adder-bites.

The various methods of treatment advocated for snake-bite are legion; many are obsolete and dangerous, giving rise to considerable sloughing of tissues and damage of important structures—for example, median and ulnar nerves. It is obvious that, short of animal experiment on a large scale, using known quantities of dried *Vipera berus* venom, it is impossible to assess the value of cortisone and antihistamine drugs; this applies even more to the numerous undesirable tissue-damaging local measures advocated, such as tourniquet, incision, and suction, rubbing in potassium permanganate crystals, infiltration with 5% carbolic soap solutions, etc. The only remedy which has stood up to the test of time is specific antivenin given early and in adequate dosage; and here the question of allergy and serum sickness must be weighed in the balance in every case of adder-bite in England.

In my very limited experience in the treatment of viper-bites due to *Cerastes cornutus* in Iraq I was impressed with the efficacy of the specific antivenin injected locally at the site of the bite, preferably through the fang punctures where the anatomical site allowed and the case was seen very early. In cases where tourniquet, incision, and potassium permanganate crystals or injections had been given by others I was distressed to see the gross destruction of tissue, even leading to sloughing of tendons and consequent serious disability.

Treatment by the tourniquet, incision of the bites, followed by the rubbing in of potassium permanganate crystals into the wound has no place when dealing with adder-bites in England and cannot be too strongly condemned; it is now obsolete in modern practice in the tropics (Reid, 1956, 1957a, 1957b, 1957c).

The application of a tight bandage above the bitten part followed by "cut and suck" immediately after the bite in an attempt to remove as much of the venom as possible is logically sound, but is extremely dangerous in lay hands and is certainly strongly contradicted as

a first-aid measure for a bite from *Vipera berus* in the United Kingdom.

Viper venom is absorbed by the lymphatics, and the best first-aid treatment is to immobilize the part by splinting or bandaging and to keep the patient at complete rest in a recumbent position. The general reaction after the bite usually ensues within one hour, and this depends on the dose of venom injected and the size and constitution of the patient.

All young children should be brought into hospital as soon as possible, and, if the case is seen very early and the site of the bite permits, 1–2 ml. of antivenin should be injected through the fang marks and the remaining 8 ml. given subcutaneously or intramuscularly into the buttocks, mixed with hyaluronidase. It is wise to give antihistamine prior to the serum.

In the case of adults or children from 10 upwards, if there are no severe general symptoms at the end of two hours from the time of the bite no antivenin is necessary, and all that is required is rest and reassurance and the administration of antihistamine drugs such as promethazine or chlorpheniramine (" piriton ").

In severe cases in adults with marked collapse and vomiting the contents of two ampoules (10 ml. in each) of antivenin mixed with hyaluronidase are injected into the buttocks intramuscularly. If the case is seen very early and the site allows—for example, calf—2–3 ml. of antivenin is injected locally through the fang marks and the rest of the antivenin used as indicated above. We have never had to exceed a total dose of 20 ml. of antivenin in any case. The symptoms of collapse and vomiting have always disappeared in two to three hours after giving antivenin. Our cases are always put on promethazine as a precaution against serum sickness and for its therapeutic effect.

If no antivenin is available and the patient's condition is critical intravenous plasma (Goddard, 1951) has been strongly recommended pending the arrival of antivenin. Ariff (1955) recommended cortisone for viper-bites, but I have had no personal experience of its efficacy.

To summarize, far more harm is done by obsolete heroic methods of treatment than by masterly inactivity and immobility together with antihistamine drugs, holding a watching brief ready to give antivenin if the general condition warrants it.

Prevention.—This should take the form of public propaganda by press, through television, and in schools, with the advice to leave all snakes in this country well alone; they are useful and harmless scavengers, and even the dreaded adder will bite only if handled or trodden on.

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FIRST INTERNATIONAL CONFERENCE ON CONGENITAL MALFORMATIONS

LONDON, JULY 18–22

[FROM SPECIAL CORRESPONDENTS]

An International Conference on Congenital Malformations, sponsored by the National Foundation (U.S.A.), was held at Church House, Westminster, from July 18–22, under the joint honorary presidency of Mr. BASIL O'CONNOR (U.S.A.) and Sir GEOFFREY MARSHALL (United Kingdom). Professor J. D. BOYD (Cambridge) was the general chairman, and Dr. G. W. CORNER, of the Rockefeller Institute, New York, gave the theme address. The conference was in eight sessions.

I.—Incidence of Malformations

The first session was on the incidence of congenital malformations. Mr. CARL L. ERHARDT (New York), whose paper was read by Dr. LOUIS HELLMAN, discussed " Pitfalls in Investigations of Aetiology." The same inciting event, he said, might result in quite different defects; yet similar defects might derive from widely varying causes. A given factor did not invariably produce the effect that was expected, and some embryos affected by a specific type of insult might die and be aborted, while others proceeded to delivery at term. Different malformations became manifest at widely different ages, and the situation was further complicated by the interplay of genetics and environment. For example, some malformations resulted from a defective gene which expressed itself only under certain environmental conditions, while acquired defects might simulate inherited defects with great exactness. Descriptive and analytical studies were both dogged by difficulties of definition and diagnosis. One of the major problems was the large number of observations required to demonstrate an association convincingly.

Professor MAURICE LAMY (Paris) said it seemed that the overall incidence of major malformations visible at birth or recognizable by anatomical examination of stillborn infants or infants who die during the neonatal period was close to 1.5%. The incidence of major malformations for all infants born after the 28th week of pregnancy and with an observation period of one year after birth would seem to be around 4–5%. This by no means represented the totality of malformations, as some only became manifest later in life. It was safe to say that the overall incidence of major malformations was higher than 5%. In countries where death due to infection and deficiency states had declined most, the mortality due to congenital malformations represented 15–20% of infant mortality as a whole. Anomalies of the cardiovascular, alimentary, and urogenital systems were more frequent in males, whereas there was a definitely increased prevalence of monstrosities, spina bifida, and meningocele among females. Hydrocephalus showed a varying sex-prevalence in different countries.

Professor T. MCKEOWN (Birmingham) restricted his discussion of the sources of variation in the incidence of malformations to five indices: maternal age; birth order; season of birth; social class; and secular variation. There were fairly well defined trends in the incidence of many malformations, reflected in an increase associated with primogeniture and increasing maternal age. There would also appear to be a distinct seasonal fluctuation in the incidence of certain malformations, and this was not related to the seasonal variation in incidence of rubella. Anencephalus was the only malformation whose incidence had been shown to be associated with social circumstances, in Scotland the incidence being remarkably higher in births to parents in the unskilled-worker class than to parents in professional and related classes. No such relation was, however, observed in Birmingham data.

A panel of experts consisting of Dr. GILBERT W. MELLIN (New York), Dr. EDITH POTTER (Chicago), and Dr. DAVID KLEIN (Geneva) then contributed to a lengthy discussion. Among the many facts and views expressed were the following: With rubella the incidence from prospective studies had been as low as 10%, whilst from retrospective studies it had been close to 100%. It was very rare to find a normal abortus in the first three months of pregnancy, and male foetuses seemed by and large to be more vulnerable to malformation.

II.—Genetic Factors

The second session was on genetic factors. Dr. J. V. NEEL (Michigan), who had conducted the Hiroshima survey, drew attention to the hazards of regarding congenital malformations as a group sufficiently unified to be studied as a whole. Only in a few rare conditions were single-gene mechanisms likely to act, while the chromosomal aberrations collectively were unlikely to constitute more than 10% of all malformations. In the preponderance of cases it was likely that they were the end-result of a confused and complex interaction between the inherited constitution and the environment. Many malformations might be manifestations of balanced polymorphisms in multigenic systems. That was to say, there were types of genes of which the presence of a few was an advantage while the presence of many might result in gross abnormality. This was not inconsistent with the all-or-none character of most malformations. As an example of such genes of mixed blessing, Dr. Neel discussed the gene determining the synthesis of sickle-cell haemoglobin: one gene led to relative freedom from falciparum malaria, two genes led to early death from anaemia. A population which favoured some of its members with one gene must condemn others with two. Dr. Neel particularly recommended the study of children of mixed marriages, whom he would expect to have a lower incidence of malformation than either parent stock.

Professor R. TURPIN (Paris), presenting a paper written with his co-author Dr. J. LEJEUNE, described the present position in relation to the chromosomal aberrations in man. Full appreciation of this paper is dependent on seeing the accompanying lantern slides. He described one new aberration, probably due to fusion between the Y chromosome and another small chromosome (21), presenting as a chromatin-positive hermaphrodite with dextrocardia.

Dr. W. M. COURT BROWN (Edinburgh) described aberrations of the sex chromosomes, reviewing the extensive experience of his research group. The sex-chromatin body was never found in the normal male, he said. In his experience there was a consistent relationship between the number of sex-chromatin bodies (Barr bodies) and the number of X chromosomes, the former being one less than the latter. This relationship held in the normal male (XY), the normal female (XX), Turner's syndrome (XO), Klinefelter's syndrome (XXY), the triple-X woman (XXX), and in the recently described (XXXY) male. A buccal smear from a male showing up to three Barr bodies had just been examined, and he felt fairly confident chromosomal analysis would show (XXXXY).

III.—Environmental Factors

The opening paper of the session on the role of environmental factors was given by Professor J. WARKANY (Cincinnati), one of the pioneer workers in the field of experimental teratology. Although a great many factors such as deficiencies of certain vitamins produced malformations in animals, the number of congenital malformations in the human population that could be shown to be due to environmental conditions accounted, he said, for only a negligible fraction of the total. In man endemic cretinism, now on the decline, was undoubtedly environmental; malformations could also be traced to infection by rubella, exposure to large amounts of *x*-radiation, and the use of aminopterin for therapeutic abortion. Nevertheless, a host of other environmental causes might exist as yet unrecognized.

The subject of maternal infection by viruses was further considered by Professor A. J. RHODES (Toronto). With rubella it appeared that the greatest risk of malformation was when the mother was infected during the first four weeks of pregnancy. So far as other viruses were concerned, there was some not very conclusive evidence that Asian influenza and mumps during pregnancy could increase the risk of malformations. In the subsequent discussion Dr. W. R. S. DOLL (London) quoted figures to show that after the Asian influenza epidemic there was a substantial increase in the number of anencephalic babies born in Scotland.

Dr. W. LANDAUER (Connecticut) considered the interplay between extrinsic factors and heredity. He pointed out that some of the differences that had been observed in the incidence of anencephaly in different population groups could be due partly to extrinsic factors, such as maternal age, parity, and nutrition, and partly to differences in genetic backgrounds.

IV.—General Developmental Mechanisms

In the session on general developmental mechanisms, Dr. EDGAR ZWILLING (Waltham, Massachusetts) surveyed present-day knowledge of inductive mechanisms. While many attempts had been made to extend analyses of inductive mechanisms to the molecular level, these had so far provided us with suggestive models, but with no details for any particular case of inductive interaction. Some experiments suggested that nucleoproteins, or fractions thereof, were important stimulators of differentiation, and it had been shown that heart microsomes might transform tissues of the chorioallantoic membrane of the chick embryo into cardiac muscle. He suggested that the mechanisms involved might consist of the diffusion of substances from one type of cell to another. These substances might be substrates for induced enzymes or molecules which might be involved in specific syntheses. On the other hand, there might be contact interaction either with transfer of particulates or without the transfer of material but with important resulting molecular reorientation. The interaction might also take place between intercellular matrices. Malformations could result either from the distortion of inductive patterns, failure of the interactants to make proper contact, loss of inductive capacity, or loss of ability to respond.

Dr. RITA LEVI-MONTALCINE (St. Louis) discussed factors controlling nerve growth and the isolation of a specific nerve-growth factor. She showed how both *in vivo* and *in vitro* a factor produced by mouse sarcoma had a marked hypertrophic and hyperplastic effect on sympathetic and sensory ganglia, but not on motor centres or parasympathetic ganglia. The agent seemed to be a protein, and the discovery that snake venom was a most potent source of this growth factor was the starting point of a whole series of investigations. Salivary grands of adult mice also produced this growth factor, and it was possible to stimulate the production of antisera which on injection led to near-total destruction of the sympathetic ganglia of new-born mammals.

Dr. C. L. MARKERT (Baltimore) reviewed present-day knowledge concerning nucleo-cytoplasmic interactions during development and was concerned principally with the results of nuclear transfer experiments, the effects of injected nuclear extracts, and the ultrastructure of developing cells. The evidence presented strongly supported the contention that R.N.A. synthesis was the exclusive property of the nucleus if not of the chromosomes themselves, and it was equally probable that most protein synthesis occurred in the cytoplasm in association with R.N.A. particulates or ribosomes. It was suggested that the fertilized egg is equipped with chromosomes largely composed of nucleohistone. Many genes on these chromosomes were not functional in the zygote, and the nucleus only played a minor role during early cleavage stages. As the chromosomes were replicated they acquired new constituents from the cytoplasm. This

activated genes to function, and the synthetic activity of the genes then resulted in the formation of ribosomes that passed into the cytoplasm. The nuclear envelopes that owed many characteristics to the activity of chromosomes might produce mitochondria and the endoplasmic reticulum to which ribosomes became attached. The activity of these organelles with the ingress of material from outside the cell resulted in a new chemical differentiation of the cytoplasm. New products arising in it passed into the nucleus and by attaching to chromosomes further differentiated them and further activated or repressed the genes. This released new products to cytoplasm, and so an oscillating interaction was established leading to differentiation and equilibrium.

A panel consisting of Dr. JAMES D. EBERT (Baltimore), Dr. HONOR B. FELL (Cambridge), Dr. V. HAMBURGER (St. Louis), and Dr. MILAN HASEK (Prague) contributed to a discussion that centred largely around questions of definition.

V.—Abnormal Developmental Mechanisms

In the first paper of the session on abnormal developmental mechanisms, Dr. J. G. WILSON (Florida) gave an excellent review of the general principles which had emerged from animal experiments. The nature of the malformation depended largely upon the stage of embryonic development at which a teratogenic agent was used, and chemically different agents could produce very similar malformations. He also emphasized that the foetus could be injured by substances which did not harm the mother ; the embryo did not live as a favoured parasite able to obtain scarce materials at the mother's expense.

Dr. F. C. FRASER (Montreal) described experiments in mice which showed that the incidence of cleft palate produced by cortisone depended upon the strain used. In other experiments he found that inactivation of nicotinamide for as little as two hours produced a high frequency of cleft palate.* Another aspect of the role of hormones was considered by Dr. E. WOLFF (Nogent sur Marne), who has carried out extensive work on the effects of the sex hormones on the development of the genital system in chicks. By the injection of oestrogens the testis of a male embryo could be changed into an ovary. Similar experiments in mammals had not met with success, but it was possible that hyperactivity of the foetal gonads could be concerned in some congenital anomalies.

VI.—Maternal-foetal Interactions

Dr. ANNE MCLAREN (Edinburgh) briefly surveyed experimental work on the effects upon the development of the young of subjecting the mother to acute or chronic environmental stress, such as thermal changes, irradiation, or immunization during pregnancy. It seemed clear from both her own experiments and the observations of others that mammals had open to them an alternative somatic maternal non-chromosomal pathway of inheritance. To what extent this pathway had been used to achieve, for example, cumulative acclimatization to changed conditions of life had yet to be determined.

It has long been known that antibody can be transferred from mother to foetus, and Dr. W. A. HEMMINGS (Bangor) outlined the ways in which this is achieved in different species. In some, such as the rabbit and guinea-pig, a transfer occurred before birth via the yolk-sac splanchnopleure ; in the mouse and rat almost all antibodies were obtained after birth via colostrum ; while in the Rhesus monkey and presumably man transfer was carried out by the placenta. The threshold activities of the human placenta for protein molecules were as yet little known, but Dr. Hemmings described how, in the rabbit at any rate, the cells of the yolk-sac splanchnopleure were quite sharply selective and could distinguish between closely similar molecules.

Dr. LEWIS THOMAS (New York) described the finding of particles of syncytium in venous blood from the pregnant uterus (from the uterine veins in 20 of 25 patients ; in the inferior venae cavae in 2 of 32 patients), thus providing *in vivo* confirmation of the phenomenon long postulated to explain their finding at necropsy in the lungs of pregnant women.

*See *Brit. med. J.*, July 16, p. 195.

VII.—Physiology and Medical Problems

Dr. D. H. BARRON (Yale) contributed the results of some experiments undertaken to analyse the factors controlling the oxygenation of foetal blood, in particular, whether the foetus itself could exert any control over its own blood supply and thus over the blood supply of the uterus. Observations on pregnant ewes had shown that exposure to various oxygen and carbon-dioxide mixtures caused no significant variation in the blood flow through the uterus.

The analysis of foetal wastage contributed by Dr. D. G. MCKAY (Boston) was based mostly on observations on early human ova and embryos. These had been obtained with accurate menstrual and coital histories from patients who had undergone hysterectomy. From 210 patients, 34 fertilized ova had been obtained, 24 normal and 10 abnormal. An interesting finding was that in some of the abnormal ova the trophoblast was abnormal as well as the germ disk.

Professor JAMES WALKER (Dundee) reported the extent of anencephaly in Dundee during the years 1950–9 as 3.3 per 1,000 births, compared with the figure of 2.9 for the rest of Scotland. This increase was not correlated with increased maternal age, but there was a significant association with parity at or beyond the fourth pregnancy. The incidence of anencephalic births was notably low in social classes 1 and 2, a finding that might well be explained by the usually lower parity in these groups. There was a clear excess of females among the anencephalic births. A rather greater incidence in 1958 was possibly associated with the epidemic of influenza in that year.

Dr. J. L. WILSON (Michigan, U.S.A.) stressed the increasing problems that infants and children with congenital malformations posed for the clinician.

VIII.—Perspectives

In the final session Professor C. H. WADDINGTON, F.R.S. (Edinburgh), spoke of the complex interactions in embryonic life, introducing the concept of canalization of development. Briefly, this might be explained on a model of numerous shallow grooves on a gentle slope in the general form of a shunting-yard, the developing embryo being regarded as a ball which coursed down its predetermined passage unless displaced into the wrong groove, when an abnormality resulted. Every ball would be buffeted about to some extent by the environment, and whether or not it was displaced would depend largely on the depth of the groove. This seemed to be very variable, uneven, and largely genetically determined. This depth Professor Waddington referred to as developmental stability. It had usually seemed reasonable to suppose that such types of stability would be greater in the presence of genetic diversity, but Professor Waddington, on the basis of his genetic studies of the fruit-fly, suggested that genetic diversity was associated with a marked diminution of developmental stability. For in the fruit-fly inbreeding appeared to reduce its malformation rate after environmental shocks.

Professor L. S. PENROSE, F.R.S. (London), spoke of the curiously complacent idea that man was an almost perfect species. The problems of being mismade would soon dominate those of acquired disease, he thought. While malformations induced by rubella were theoretically preventable by early infection, and some reduction in incidence of mongolism and Klinefelter's syndrome would follow earlier childbearing, and some other abnormalities might be reduced if the parents could be correctly informed of the recurrence rates, it was in general difficult to see how increasing knowledge would lead to a reduced incidence.

HUMAN ARTIFICIAL INSEMINATION

FEVERSHAM COMMITTEE'S REPORT

[FROM OUR LEGAL CORRESPONDENT]

The report of the Departmental Committee* on Human Artificial Insemination was published last week (Cmnd. 1105, 1960. H.M.S.O., price 5s. 6d. net). The Committee was appointed in September, 1958, jointly by the Home Secretary and the Secretary of State for Scotland with these terms of reference: "To inquire into the existing practice of human artificial insemination and its legal consequences and to consider whether, taking account of the interests of individuals involved and of society as a whole, any change in the law is necessary or desirable."

Recommendations

The majority of the Committee summarize their recommendations as follows. Two members of the committee, however, Mrs. Jay and Mr. Ross, signify their disagreement with recommendation 2(*e*) below in a memorandum of dissent.

1. Artificial Insemination by Husband

The fact that a live child has been born as a result of artificial insemination of a woman with the seed of her husband should be a bar to proceedings by either spouse for nullity of marriage on the ground of impotence.

2. Artificial Insemination by Donor

(*a*) Acceptance by a wife of A.I.D. without the consent of her husband should be made a new ground for divorce or judicial separation, and in England these circumstances should also enable a husband to take matrimonial proceedings in a magistrates' court.

(*b*) The law should not be amended to permit a decree of nullity of marriage to be obtained on the ground of sterility.

(*c*) The fact that a live child has been born as a result of A.I.D., to which the parties to the marriage consented, should be a bar to proceedings by either spouse for nullity of marriage on the ground of impotence.

(*d*) The law of Scotland should be amended to give a child born of A.I.D., to which a husband has consented, the same rights of maintenance as an adopted child, and in England the child should be entitled to claim that provision for his maintenance be made out of the deceased husband's estate.

(*e*) There should be no amendment of the laws relating to legitimacy or registration of birth.

(*f*) The law should not be amended to enable a wife to take proceedings for divorce on the ground that her husband has donated semen for the purpose of A.I.D. without obtaining her consent.

(*g*) While the practice of A.I.D. is strongly to be discouraged, it should not be declared criminal or be regulated by law.

A.I.D. in Britain

Besides considering the problems involved, the Committee have made a survey of the origins, practice, technique, legal consequences, and psychological implications of the practice of A.I.D., A.I.H., and A.I.H.D. (artificial insemination with the combined semen of the husband and a donor).

Although the earliest recorded case of human artificial insemination was a case of A.I.H. performed by John Hunter in about 1790, the development of the practice had been at most sporadic until the post-war years. The subject was debated in the House of Lords in 1943, with particular reference to the problems encountered in the U.S.A., which had the highest proportion of A.I.D. conceptions in the world. Interest and activity in this sphere was further encouraged during the next two years by articles in the medical press, including one in the *British Medical Journal*,† which gave what was apparently the first comprehensive account of the technique and results achieved. Even so, the Committee estimate the number of practitioners in Great Britain regularly engaged in the practice of artificial insemination to be probably rather fewer than 20, and the number of A.I.D. children born in the last 20 years to be not more than 1,150.

Although practitioners took considerable care in selecting persons suitable for A.I.D., not very much was known of the psychological results of A.I.D., owing to inadequate follow-up. There were only between 1,000 and 9,000 marriages each year which could physically benefit from A.I.D.: but a very high proportion of the persons involved would be psychologically or otherwise unsuitable, and as many would be antagonistic towards A.I.D. The usefulness of A.I.H. was even more limited. However, A.I.H. might become more popular if the technique of separating spermatozoa for the purpose of determining the sex of the child was perfected. A technique of using a husband's spermatozoa with a donor's seminal plasma was also being studied.

Matrimonial Law and Legitimacy

As the law at present stood, the effect of A.I.D. in matrimonial law was in doubt on some points. It was decided law that a wife's submission to A.I.D. would amount to approbation of her marriage and bar her from obtaining a nullity decree on the ground of wilful refusal or incapacity to consummate, so long as she submitted knowing the facts and the law. It was not clear whether submission to A.I.D. amounts to condonation of a matrimonial offence, and whether it amounts to adultery was seriously in doubt, though the better view would seem to be that it does not. In some circumstances, submission to A.I.D. might amount to cruelty, and might justify a husband in leaving his wife.

There was no doubt that a child born by A.I.H. is legitimate, and one born by A.I.D. illegitimate. However, the presumption that a child born to a wife during wedlock is legitimate was difficult to rebut, and in the case of A.I.H.D. would be impossible to rebut, unless it were shown that the husband's semen was totally infertile or that the blood-group of the child was inconsistent with the fatherhood of the husband. The husband was bound to maintain children conceived by A.I.H., and must also maintain children conceived by A.I.D. whom he had accepted into the family. It was most unlikely that a donor would fall under any duty to maintain the child.

A child known to be illegitimate must be registered on birth as such. In the case of A.I.D., the presumption of legitimacy would enable the person registering the birth to register the husband as the father unless he believed that there was no real possibility that this might be so. One who made a false registration knowingly was guilty of perjury. It had been suggested that persons assisting in A.I.D. are guilty of a criminal conspiracy to produce an illegitimate child. It seemed to the committee that this was unlikely unless the intention of the parties was to defraud.

A.I.H. and the Law

The Committee did not think that A.I.H. ought to be prohibited by law, although it recognized it to be distasteful to large numbers of persons, including Roman Catholics. (Some of the latter, however, did not object to "assisted insemination," that is, insemination following upon intercourse using semen deposited in the vagina.) The only recommendation concerning A.I.H. is set out in the summary of the Committee's recommendations above, and was made in the interest of the child solely. The Committee did, however, contemplate the possible need for legislation forbidding A.I.H. after the husband's death if that became possible, and did recommend that progress in the use of A.I.H. for

*Earl of Feversham (*chairman*), Dr. L. Priscilla FitzGibbon, Mrs. Peggy Jay, Dr. D. T. McDonald (died June, 1959), Dr. S. R. Mathews (appointed July, 1959), Mr. R. Risk, Mr. J. Ross, Mr. Justice Stevenson, Professor R. E. Tunbridge, and Mrs. H. Whitley.

†Barton, M., Walker, K., and Wiesner, B. P., *Brit. med. J.*, 1945, 1, 40.

sex determination should be kept under review lest, on becoming widespread, it should upset the balance of the sexes.

Social Considerations

In the Committee's discussion of the effect of A.I.D. on the relationship between husband and wife, the only point which emerges clearly is that no general rules could be discovered: in some cases the effect was beneficial, in others detrimental. However, in the course of their discussion the Committee made recommendations 2(*a*) and (*b*) (above), and also expressed their unqualified disapproval of artificial insemination of single women.

The Committee were much concerned by the grave difficulties to which the A.I.D. child is exposed, and on this ground alone would discourage A.I.D. But in order to protect A.I.D. children in some measure, the Committee made recommendations 2(*c*) and (*d*). However, the Committee were unable to recommend that A.I.D. children should be made legitimate: from this view two members (Mrs. Jay and Mr. Ross) dissented, accepting the view of the Law Society.

The B.M.A.'s view that the practitioner in A.I.D. needs to have considerable knowledge in gynaecology, male infertility, psychological medicine, and human genetics, received the support of the Committee, who were particularly concerned by the difficulty in selecting suitable parents for A.I.D. For this purpose an extensive knowledge of psychological medicine, together with a great deal of background knowledge of the family, was required. Above all, there was a pressing need for research in the follow-up of A.I.D., if the practice was to continue.

The Committee concluded that A.I.D. is undesirable because it is a danger to the institution of marriage and to the resultant children; it dissociated responsibility for rearing children from responsibility for their procreation. And, in view of the weight of medical opinion against its practice, it was questionable whether A.I.D. should fall within a doctor's proper responsibilities. However, the Committee do not recommend the prohibition of A.I.D., as the practice is rather a matter for the individual conscience, and such prohibition would in any case be unenforceable. Nor do the Committee recommend its regulation, either by statute or by the profession. For one thing, regulation might be understood to imply a degree of official recognition which would be undesirable.

The report ends with an appendix on the law and practice overseas and a list of those who gave evidence to the Committee.

USE OF ORAL CONTRACEPTIVES

STATEMENT BY MEDICAL ADVISORY COUNCIL* OF THE FAMILY PLANNING ASSOCIATION

We have been asked by the Family Planning Association to publish the following statement by its Medical Advisory Council.

The Medical Advisory Council of the Family Planning Association has given careful consideration to the question of the advisability of using the progestational steroid norethynodrel together with an oestrogen as a contraceptive under the conditions planned for clinical trials in some of its clinics, and is satisfied that it is perfectly safe for use in the way planned.

Administration

Patients who volunteer and who come within the age range, 25 to 24 years, and who have one or more children, thus proving their fertility, will be given one tablet of norethynodrel, 2.5 mg., containing ethinyloestradiol 3-methyl ether, 0.1 mg., daily from the fifth day of the menstrual cycle for twenty days. The tablets will then be stopped and resumed again after an interval to allow for menstruation. Though a preliminary assessment will be made in six months, the trial will be continued for a year and patients will be followed up wherever possible for five years. The efficiency of this dose of norethynodrel has already been established in over 1,000 cycles of administration. The object of the present trials is to work out improved methods of administration and to find the best possible practical instructions for patients.

Side-effects.—Side-effects are known to occur in about a third of all patients who start taking norethynodrel. The incidence varies somewhat with the dose and with the dose of oestrogen. One of the objects of these trials is to determine the doses of norethynodrel and of oestrogen which will produce least side-effects. The majority of these are gastro-intestinal symptoms—nausea, vomiting, headache—and are believed to be due to the oestrogen. They clear up spontaneously, however, after one to three cycles of administration and are relieved by antacids. Break-through bleeding occurs in about a third of the patients and can be bewildering to the patient and make the administration instructions more difficult. This, however, is quite harmless and settles down after three to four cycles. While previous investigators have increased the dosage to prevent break-through bleeding when it has threatened, we are advising patients to ignore spotting but to stop taking the pills if frank bleeding occurs and to start treatment again on the fifth day as if this had been a normal bleeding. There is no proof that libido is affected. In the majority of patients no change is observed, a few notice an increase, a few decrease in roughly equal numbers. Some patients notice tenderness and tumescence of the breasts at the beginning, but this is reduced in later cycles and in some patients there is a noticeable reduction in breast fullness and size. The majority of patients notice an increase in weight to begin with, which settles down to normal after two to four cycles of administration.

What is the Risk of its Being Carcinogenic?

The effect of the administration of progesterone and oestrogen separately and together have been considered. Oestrogens are known to cause abnormal changes in certain circumstances, particularly in the mammary glands. This is known in certain strains of mice which are prone to it anyway, but has not been shown in other experimental animals. Overgrowth of fibrous tissues are known which are definitely not malignant and are entirely suppressed by progesterones. There is no evidence of malignant growth. In any case, while continued stimulation may cause cancer in animals, interrupted administration is not usually considered to do so. In humans, though the incidence of cancer of the uterus is higher in women who have a high continuous level of endogenous oestrogen production, there is no evidence of administered oestrogens having this effect. No one has shown that exogenous administration has ever produced cancer.

When progestins are administered alone there is no evidence that any changes in organs take place which can give rise to malignant growths. When oestrogen and progesterone are administered together progesterone would seem to have a protective effect in humans as well as in guinea-pigs. The progesterone protects the animals from any adverse effects of oestrogen, and the balance of these pills is progestogenic instead of oestrogenic.

If these pills are administered to someone who already has cancer of the breast or uterus, it would appear that they would not cause harm and might have a tendency to arrest it.

Long-term Effects

The possible long-term effects of prolonged pituitary inhibition have been studied. In animals when pituitary activity is inhibited its effects are all entirely reversible, with the exception that, if the oestrogen is administered continuously to a rat for two-thirds of its life, pituitary adenoma may appear. In women, oestrogens have been administered continually for medical reasons over at least eight continuous cycles and sometimes over years, yet when medication has stopped ovulation has taken place in the next one or two cycles. Thus even constant administration of these

*Sir Russell Brain (chairman), Sir Dugald Baird, Sir Andrew Claye, Mr. D. B. Fraser, F.R.C.S., Dr. J. A. Fraser Roberts, Professor D. V. Hubble, Mr. I. M. Jackson, F.R.C.S., Sir Aubrey Lewis, Professor N. F. Morris, Professor W. C. W. Nixon, Sir James Paterson Ross, Mr. J. A. Stallworthy, F.R.C.S., Dr. G. I. M. Swyer, and Dr. J. Sutherland.

steroids over prolonged periods of time does not appear to interfere with ovarian function on a permanent basis. Then, too, norethynodrel has been administered cyclically for contraceptive purposes to over 1,000 women during 15,000 cycles of medication: the trials have in fact been going on for over five years altogether, and so far there does not appear to be any long-term effect on the ovary or pituitary. Ovarian biopsies have been obtained from women who after using norethynodrel as a contraceptive for some time have wanted to be sterilized. These women were always sterilized during the last two weeks of a cycle and were medicated right up to the time of operation. None of these ovarian biopsies has ever shown a trace of corpus luteum. There has been no correlation between the numbers of primordial follicles and the duration of administration of the oral contraceptive.

Data available in the literature show that subsequent fertility is not affected whether after short or long courses of medication. So far as long-term effects on other endocrine glands are concerned, there appears to be no substantial effect on other glands, except possibly on the adrenal cortex, in which there is an average lowering of excretion of its products, which on intense study has been found to involve some alteration in the metabolism of hydrocortisone. There have been no symptoms of hydrocortisone deficiency in these women, and the blood concentration is well above normal level.

Recently, the United States Food and Drug Administration approved an application for the use of norethynodrel as an oral contraceptive, showing that they consider the information submitted indicates that norethynodrel is safe for use under the conditions which have been covered by the application, which is the use of one 10-mg. tablet daily for 20 days each menstrual cycle, with the recommendation that such use be restricted to not more than 24 consecutive cycles for the time being. It will be seen that this dosage is four times the dosage being used for trials in this country.

Hirsuties and Liver Damage: Long-term Effects

Some of the progestational steroids are androgenic, but this is not so with norethynodrel, which is oestrogenic; there is therefore no danger of this with the preparation we are using.

Some new synthetic steroids have been found to cause liver damage, but these have been androgens such as methyl testosterone. As a routine precaution liver-function tests in representative groups of patients and also in controls have been carried out. Normal liver function is indicated by the results where norethynodrel has been the steroid administered.

Nova et Vetera

CAUSERIES ON ANAESTHETICS

The title of this witty but also very serious book is perhaps a little misleading.* Dr. Sykes retired from the profession of anaesthetist some twenty years ago. Since then he has collected all the early records that he can of his art. He has not only gone deep into the subject but has attacked some very unusual, and perhaps unexpected, sources. This is not in any sense a history of anaesthetics but a series of *causeries* on its early records, and it is therefore hard to review adequately, though it is very readable.

Dr. Sykes has some bugbears, both human and technical. Among the human ones are Syme, father-in-law of Lord Lister and, for a few unhappy weeks, professor of surgery at University College, London. Among the technical ones, the prime bugbear is carelessness in the first stage of chloroform anaesthesia, especially in unprepared patients. It may be supposed that under modern conditions this offence is as dead as the human offender. Older medical men, among whom the reviewer reluctantly admits he is to be numbered, can remember times and places where any "qualified" man was supposed to be equipped to give any anaesthetic and, except for the omission of a meal, no pre-operative treatment was usual. The crude anaesthetic death-rate was, Dr. Sykes believes, of the order of 1 in every 2,500 operations, but this probably does not include the deaths from ether pneumonia. It is perhaps not realized how hard it is to get any statistics of an earlier period because of the minute number of operations performed. Thus Dr. Sykes says:

> "In the pre-anaesthetic era the number of operations in the large hospitals was about fifty a year. Not one of the London hospitals had more than one operating session a week. In 1825 *The Lancet* said of St. Thomas's 'The only operation performed here this week was that of lithotomy, . . . completed in about three minutes.'"

By 1862, after anaesthesia was well established, but before the coming of antiseptics, the numbers rose to about seven a week. St. Bartholomew's had 329 operations in the year with 32 deaths, Guy's had 541 with 44 deaths, Leeds General Infirmary 211 operations with 16 deaths. In none of them, of course, were any of the operations abdominal. By 1868, at the very beginning of Listerism, St. Bartholomew's actually had two operating sessions per week, and 534 operations with 60 deaths.

The idea than anyone could give an anaesthetic was unconscionably slow in dying. People would not admit that any appreciable knowledge, training, experience, or skill were required, despite the constant and steady stream of reports of chloroform deaths. Some writers ignored evidence and said that the risk was trivial. Lauder Brunton, a physiologist of high repute, stated in 1895:

> "The dread of pain has of late been replaced by a dread of the anaesthetic which would relieve it, and many people will now suffer the short, but extremely severe pain caused by the extraction of a tooth rather than run the trivial risk of using an anaesthetic."

The general public had, however, realized that "although the percentage of deaths might be numerically small, each fatality was 100% dead, a fact which appears to have escaped the attention of the physiologists"—a rather severe criticism by a particularly humane physician.

Within the reviewer's medical memory it was often stated that chloroform was much more safely given in Scotland than in England. This persistent legend was, as Dr. Sykes shows, a hangover from the days of Syme and Simpson. In 1855 Syme wrote:

> "It is said in London that the risk of giving chloroform is so great that it is only justifiable in operations accompanied with extreme pain, or where stillness on the part of the patient is essential, and that the greatest caution is required in its administration; here we say that, with moderate care, it is perfectly safe. In this theatre chloroform was first administered in public by Dr. Simpson, seven years ago; since then it has been *almost daily* given here, yet we have not had a fatal case."

To surgeons accustomed to the old pre-anaesthetic routine of one short operating session a week for the

**Essays on the First Hundred Years of Anaesthesia.* By W. Stanley Sykes, M.B.E., B.Chir.(Cantab.), D.A. Volume I. (Pp. 171; illustrated. 30s.) Edinburgh: E. and S. Livingstone, Ltd. 1960.

whole hospital staff, the spate of new work produced by painless surgery might make three times a week seem "almost daily." If this were the case, the total number in seven years would be just over a thousand.

"A little piece of evidence turned up," writes Dr. Sykes, "which confirmed my estimate. It shows that Syme was exaggerating when he used the vague expression 'almost daily.' Mr. Annandale, who became one of Syme's successors, wrote a letter giving the exact number of operations at the Edinburgh Royal Infirmary 'for November, 1862.'

"In it he sought to indicate the wealth of material available at that institution. The figures were: Mr. Syme 13, Mr. Spence 8, Mr. Gillespie 3, Professor Miller 2 . . . giving an average of just over 300 a year. This was certainly a vast—probably six-fold—increase over the figures of the pre-anaesthetic era. But it was nothing out of the ordinary, as Mr. Annandale appeared to think. Other hospitals had experienced the same increase. Thus at St. Bartholomew's 300 operations were performed in 1860.

But all these are sad, forgotten, far-off things. There are surely faults and disadvantages in over-specialization, but it is a necessity in our modern scientific world. How to meet these faults and failings is the problem of the future. But sure it is that no specialty has justified itself more than that of anaesthetics. Of that, Dr. Sykes's book will satisfy anyone, and will also provide him with plenty of good and entertaining, if somewhat discursive, reading.

CHARLES SINGER.†

ARCHETYPAL PHYSICIAN

A point on which all historians of medicine are at one is that medicine, as a scientific discipline, began with the Greeks. This is noteworthy in that, in the earliest Greek medical works, the number of examples in which cause and effect are manifestly related was pitifully few. Thus for the Greeks scientific medicine was rather a way of belief, a faith, even perhaps a myth. It had to contend with other myths, and not least with that of Asklepios, better known by his Latin name Aesculapius. Most of us have learned that Asklepios was originally a real being, a physician and father of two physician-sons, Podalirius and Machaon, some of whose exploits are related by Homer. Professor Kerényi seeks to show,* and has succeeded in showing, that the myth of Asklepios is far older than Homer and that we must now modify our view that Aesculapius was but a deified doctor. He believes that it entered the Greek world long before Homer, perhaps before 1500 B.C., and probably from the north, radiating from Trikka in Thessaly. Later it became widely diffused throughout the Roman world, with a centre at the metropolis and reaching even to Engand. Ultimately it attained almost the dimensions of a religion and occasionally the figure of Asklepios was even mistaken for that of Christ.

Nowadays we live in a world of specialties. Each specialism develops its own terms, almost its own language. Among such specialties is mythology, of which Professor Kerényi is an eminent exponent. The readers of this journal would not wish us to introduce them to the technicalities of that world, so distant from that of medicine, or even from the history of medicine. It must therefore suffice here to say that Professor Kerényi considers that in the legend of Asklepios his mother represents the dark nocturnal world of material birth where gather the seeds and energies for a second and more spiritual birth. The parallel to elements of Christianity is obvious. In the primordial world of mythology the vehicles of such seeds and forces frequently appear as contradictory figures, often half or wholly animal. One of these is in all our memories. He is Chiron, the wise and good Centaur who, according to a persistent legend, taught his art to Asklepios. But there are other semi-human beings associated with Asklepios. All these—and there are many—make the rationalism of the Hippocratic Collection even more remarkable than we thought it.

We permit ourselves one grumble. Technical terms are needed but, when not needed, are pests. This book attempts to inject into English the word *mythologem*. If it is to mean in English what it means in Greek, it is simply the telling or relating of a myth, and is frankly hideous and unwelcome and best forgotten. May it never enter the English dictionaries!

CHARLES SINGER.†

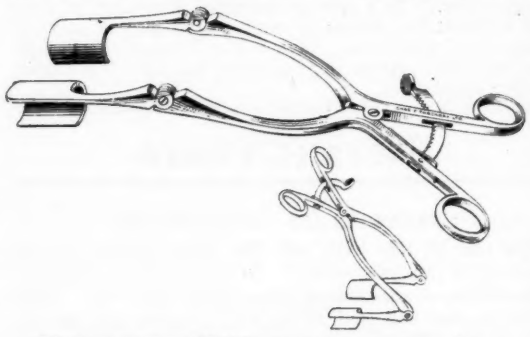
*Asklepios. Archetypal Image of the Physician's Existence. By C. Kerényi. (Pp. 151+xxvii; illustrated. 30s.) London: Thames and Hudson. 1960.

†These reviews were received shortly before Professor Singer's death on June 10.

New Appliances

MAYO'S GOITRE RETRACTOR MODIFED FOR USE AS A STERNUM SPREADER

Mr. KINGSLEY LAWRANCE, of the Department of Thoracic Surgery, the General Infirmary at Leeds, writes: Dr. J. Kirklin, of the Mayo Clinic, first altered the Mayo goitre retractor to adapt it for satisfactory use as a sternum spreader, and in the thoracic surgical department at Leeds we have modified it still further. The instrument is made on the same principle as the Mayo retractor, but with the following modifications. (1) The maximum opening of the inner, curved portion of the blades is not less than 8½ in. (21.6 cm.). (2) When the instrument is in use the bows and shanks, including the portion up to the hinges, can be folded right over to approximately 135 degrees as compared with the 90 degrees angulation normally found on a



Mayo retractor modified for use as a sternum spreader.

standard Mayo retractor. The hinges are blocked to prevent angulation in the opposite direction. (3) The arms measure 4 in. (10 cm.) overall from the distal end of the blades to the centre of the first joint. (4) The blades are solid, being 1½ in. (3.8 cm.) wide, but of the same curvature and depth as the Mayo pattern. (5) The overall weight is approximately 50% greater than that of the standard Mayo retractor.

The resultant instrument is shown in the diagram. It was necessary to increase the various dimensions of the retractor to provide satisfactory exposure of the heart and great vessels through the midline sternal splitting incision. The

weight of the instrument was increased so that it could be used in adults as well as children, and by making the blades solid not only is damage to tissue avoided, but sutures do not become entangled. The increase in angulation to 135 degrees permits access to the groin in small children (for femoral artery cannulation in by-pass perfusion) without removing the retractor and without danger of the handles inadvertently falling.

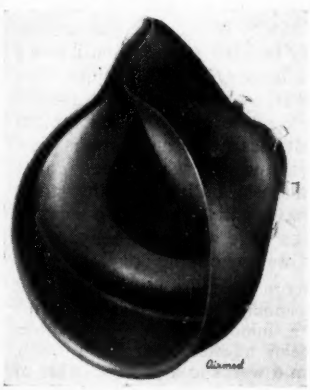
We have used this retractor to spread the sternum in over 30 patients who have had by-pass perfusion operations. Their ages have varied from 3 to 45 years, and the instrument has proved satisfactory for all sizes of patient. We find it a great improvement on any other retractor we have used previously for this purpose; in addition to the points mentioned above, it is a very "discrete" retractor, in that it does not project into or invade the incision.

The retractor was made for us and can be supplied by Chas. F. Thackray, Ltd., of Leeds.

A NEW FACE MASK

Drs. E. K. GARDNER and J. D. ROCHFORD, consultant anaesthetists, Barnet Group of Hospitals, write: The edentulous patient constitutes something of a problem for general anaesthesia with a mask; and we do not believe that endotracheal intubation should be an essential part of every general anaesthetic.

A search was made for a mask having the following features: (1) an outer flange to fit snugly below the mandible, (2) an internal flange to rest lightly on the anterior border of the masseter, (3) a good fit over the bridge of the nose, and, preferably, (4) to provide a seal against reasonable positive and negative pressures.



Our search proved unsuccessful, and we invited Airmed to develop a new mask because we felt that their specialist knowledge of masks used in the field of anaesthesia and aircraft might provide the solution.

After much experimenting and testing of prototypes we have selected a mask with a fairly rigid "shell" but with soft, pliable rims and chin elevator, and having all of our original requirements. The dead space is small and the mask can be sterilized by boiling.

The mask is a one-piece moulding in antistatic rubber, known as the "duoseal," and is supplied complete with a universal harness ring and bush; the latter accommodates both the English facepiece and the American Heidbrink male fitting. The mask is available in medium size only at present, and is considered suitable for edentulous men and women, and women with teeth. Two other sizes will be available later—large for ordinary men, and small for smaller faces generally.

The duoseal may be obtained from Airmed Limited, 16, Wigmore Street, London, W.1, and at Harlow, Essex.

A first supplement, covering the 1959 literature, has been published to the annotated bibliography of the constituents of tobacco smoke. During last year a number of compounds, not previously found, have been identified in it. Perhaps the most unexpected are a number of amino-acids, sugars, and long-chain fatty-acid esters of sterols. (Tobacco Manufacturers' Standing Committee, 6–10, Bruton Street, London, W.1. Research Papers No. 3.)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Bretylium Tosylate

"Darenthin" (Burroughs Wellcome)

This hypertensive drug has been the subject of a report in this column (February 13, page 496). A potentially serious complication of treatment with it has recently been reported in a statement issued by the manufacturers:

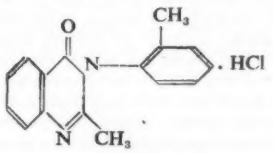
"It has just been reported to us that the condition of a few patients suffering from malignant hypertension and treated with 'darenthin' has seriously deteriorated between visits to the clinic. This has been attributed to the sudden and rapid development of drug tolerance. We accordingly recommend that patients at present being treated with 'darenthin' should have blood pressure readings taken at frequent intervals so that any rise in pressure may be immediately detected."

The manufacturers state that investigations are being carried out to determine whether the risk of tolerance can be reduced by simultaneous use of darenthin with chlorothiazide or a ganglion-blocking drug.

Methaqualone

"Melsedin" (Boots)

Chemistry.—Melsedin is 2-methyl-3-*O*-tolyl-4-quinazolone hydrochloride and has the following structural formula:



Pharmacology.—This is a recently introduced, orally active, non-barbiturate mild hypnotic.

Therapy.—In adults the hypnotic dose is usually 150 mg., but occasionally 300 mg. may be required at first in some patients. Sleep usually occurs within 40 minutes and lasts for six to ten hours. In children over 7 years the hypnotic dose is half the adult dose. The drug is also active when given in a suppository. In therapeutic doses there are no reports so far of a depressant action on the respiratory, cardiovascular, or haemopoietic systems, nor are there any reports of damage to liver or kidney. Skin rashes are said not to occur. To date there is no evidence of the development of tolerance or addiction to methaqualone. The drug is excreted rapidly, therefore cumulative effects are unlikely. Hangover effects occasionally occur.

It is impossible at present to state precisely how methaqualone compares with other hypnotics, but present indications suggest that it is slightly less active and less reliable than cyclobarbitone and quinalbarbitone. The addition of 25 mg. of chlorpromazine makes it more active and more reliable as a hypnotic. The absence of reports of skin rashes with methaqualone makes it a possible alternative mild hypnotic for barbiturate-sensitive patients. There is some evidence that this drug is useful as a potentiator of the analgesic and antitussive actions of codeine and dextromethorphan.

Side-effects.—Gastric upsets have occurred in a small percentage of patients receiving this drug, while some patients are resistant even to the largest (300 mg.) hypnotic dose, and may only become confused and giddy and develop a headache. Occasionally mild stupor has occurred on the morning after a hypnotic dose. As with barbiturates, alcohol increases the depressant effect of methaqualone on the central nervous system.

N.H.S. Basic Price.—100 150-mg. tabs., 15s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Doctors' Letters

SIR,—Medical consultations to-day are largely matters of correspondence. Opinions and impressions of doctors' personalities and qualities are built up from the letters that pass to and from G.P. to consultant and vice versa. Often years pass without the two ever meeting each other. All this is to be deplored, but with the ever-increasing pace of and developments in medicine this situation has to be accepted, endured, and improved. Obviously these letters are, or should be, personal matters and are bound to vary in length, breadth, and usefulness, but some purpose might be served if some basic points were defined and discussed.

The G.P.'s Letter

The quality of the individual family doctor often tends to be judged by the hospital doctors by the letters he writes to them. There is undoubtedly much truth in this, and it is very likely that the standard of general practice in any area could be readily assessed by an analysis of a random sample of such letters. In view of the possibility of G.P. merit awards there is some point to this.

The writing of the letter may take place in a variety of situations, as on a visit, during a consultation, or at leisure at a quiet time. Typing or writing depend on personal preferences. The paper on which the letter is written is also a personal matter. In most cases standard note-paper is used, but there has been a tendency in recent years for the use of partly printed forms which save time but which add an impersonal touch. All of us can quote the "howlers" of "letters" written on visiting cards with "please see and treat" requests, on E.C.10 slips, and other bits of paper. One can only hope that comment and discussion will result in re-education.

The contents need to be brief but should presumably contain the details of the G.P.'s problems and reasons for referral and what he (the G.P.) expects of his hospital colleagues. Details should also be given of the present and past histories, together with the treatment given and information on relevant personal, social, and family characteristics.

The Hospital Letter

A visit to a consultant is an important event in the medical life of an individual and deserves to be commemorated by a suitable record. These records filed in the patient's medical record envelope give valuable information, especially to new doctors when that patient moves. It must be remembered, however, that the size of these envelopes ($7\frac{1}{4} \times 4$ in.) is not designed to fit the variety of shapes and sizes of the hospitals' writing papers. These fit with difficulty and in time bulge and split the envelopes. There is one size of envelope that *does* fit easily, namely the 9×5 in. quarto. I would like to make a plea for hospitals to *standardize the sizes of their writing paper to family doctors to* 9×5 *in.* to ease our difficulties.

A further plea is for letters to be written and posted within 48 hours of the patient being seen or on discharge from the wards or after death. This applies with particular force to *casualty departments.* Except on rare occasions the family doctor never receives a report on those of his patients seen and treated in casualty departments. They may have been given antibiotics or other drugs and sera which may well have a bearing on their future management, but the family doctor never hears of this. Lack of time or staff are inadequate excuses for these discourtesies.

What does the G.P. hope to see in the hospital letter? First, he hopes for answers to the problems he has raised, be they diagnostic or therapeutic. He also hopes to receive brief notes of the consultant's clinical findings and the results of investigations. It is essential for the family doctor to be informed as to what the patients and/or relatives have been told by the consultant and his colleagues in hospital.

Just as the consultants build up opinions and impressions of family doctors from the letters they receive, so in return do the family doctors. Helpful letters written on time, brief and to the point, with all the necessary facts, go a very long way to developing and maintaining good relations. The family doctor particularly appreciates the personal letter from the consultant reporting interim progress on the "interesting case." This applies with special force to the worrying acute surgical emergency that the family doctor has sent in. A letter from the consultant or registrar who has operated on it is most welcomed.

These opinions may be personal, but they refer to an important subject that is all the better for an occasional airing and discussion in the correspondence columns.—I am, etc.,

Beckenham, Kent. JOHN FRY.

Is This Whooping-cough?

SIR,—Since immunization against pertussis was introduced about ten years ago, the incidence of the disease has gone down considerably. In the last six years, in general practice, I had rarely heard a child whoop, though the sound was very familiar to me when I was a houseman for a year at a large children's hospital nine years ago. I have, however, in recent years frequently treated a child with a spasmodic cough whose mother said the child whooped, but because pernasal swabs grew no *Haemophilus pertussis,* and the white-blood count was not typical of the disease, I dismissed the story. Paediatricians whom I have had occasion to consult with some of these children have agreed in denying the possibility that the illness was whooping-cough.

This year I have seen more than the usual number of children with such a spasmodic cough; indeed, in my practice there has been a minor epidemic—more than 1% of the total practice being affected (over 30 in 3,000). Their ages have varied from 6 weeks to a young mother of 22 (one man of 55 also had a typical cough, but no whoop, and I doubt if his case is relevant); most of the patients have been between 4 and 10 years. None of the actual whoopers have been immunized against pertussis by me, and I do not know their immunization state, but some of the lesser spasmodic coughers were given a full course by me. Twenty children have had a pernasal swab taken (by a competent technician or a pathologist—usually at a local children's hospital) and a white-blood count performed. None of them grew *H. pertussis*; only one child (a girl of 4 who had not been immunized against pertussis) had a typical blood count (75% lymphocytes in a total of 20,000). This child also had a collapse of both lung bases on *x*-ray.

What is interesting, however, is that twelve of the others have had a slight increase in the number of lymphocytes in a total count of 8,000–11,000. Most of the children are over the age of 4 years, though the results are still within the range of normal. I also remember that this lymphocytosis occurred in the occasional cases of spasmodic coughing I investigated in previous years—indeed, I always suspected the possibility of tuberculosis when I saw the count.

I have asked several paediatricians and other G.P.s whether they have had any cases of proved whooping-cough this year, and they tell me their findings have been like mine. The pathology departments of the children's

hospitals where I have made inquiries say that they have not grown *H. pertussis* in any large quantities ; they have not usually attempted to correlate the bacteriology with the blood picture. On the other hand, the numbers of notifications of pertussis are higher this year (in London, at any rate) than recent years, though by no means at epidemic level. What are the findings in other parts of the country ? Has pertussis altered its pathology ? Or are we seeing a new disease ? Or has immunization protected our children against *H. pertussis* (with its associated blood picture), leaving us with the basic (viral ?) infection on which the haemophilus was a secondary invader ?—I am, etc.,

London, W.12. STUART CARNE.

Breast Abscesses in the Puerperium

SIR,—In their article on breast abscesses in the puerperium (May 28, p. 1603) Drs. D. H. K. Soltau and G. W. Hatcher suggest that an important preventive measure to be taken in a maternity department experiencing cases is the cessation of breast-feeding. This appears a counsel of despair. Having allowed the babies, born free of bacteria, to become colonized with non-maternal strains of highly virulent antibiotic-resistant staphylococci, it is now suggested that they are too dangerous for their mothers to suckle. It seems that both mothers and babies are to be deprived of a normal relationship for an indefinite period. We believe this to be quite unnecessary and that it is possible to maintain babies effectively free of epidemic strains if sufficient bacteriological control is exercised.

We consider the babies' noses to be not only the principal source and reservoir of staphylococci but also the most sensitive indicator of environmental contamination. As reported in our previous letter (August 18, 1959, p. 192) we have found that if nasal swabs are examined from all babies on discharge, any "build up" of epidemic antibiotic resistant strains can be detected in time for action to be taken. This consists in the suppression of staphylococcal colonization of all the babies' noses by the administration of neomycin drops (one drop of 0.5% neomycin sulphate in isotonic neutral solution in each nostril after each feed) throughout the baby's stay in hospital. When this routine is continued for a sufficient length of time (3–4 weeks), babies subsequently born in the department acquire a normal flora. At no time under this regime is it dangerous for the mother to feed her baby.—We are, etc.,

W. H. J. BAKER.
D. R. CHRISTIE.

Department of Pathology,
County Hospital, Hereford.

Sewage at the Seaside

SIR,—It is good to see the *B.M.J.* give prominence to a letter about seaside sewage. Medicine is here the mainspring to action. The same applies to estuarial pollution. Medical opinions have need to be fully expressed and, eventually, appropriately formulated by a professional body. Many will echo Dr. J. Cantor (July 16, p. 228): "the position would appear . . . perfectly straightforward." A walk on the sands near this city is likely to end in nausea and the scrubbing of shoes. Human excrement lies everywhere. The crowds swarm and the children play. Into the sea the river looses its stinking cargo, the ordure of Tyneside. Doubtless many beaches elsewhere can be seen to be so affected.

The M.R.C. report (Memorandum No. 37) is entitled "Sewage Contamination of Bathing Beaches in England and Wales." As a precise study in the bacteriology of beach sea-water it is of indispensable value. It does not deal with beaches in the sense of the strand. The report describes paratyphoid in bathers "infected by direct contact with undisintegrated faecal matter." It further says: "The Committee has not yet been able to make a careful study of the effects of comminution or of other modifications in sewage disposal." The conclusion of this report is: ". . . the risk to health of bathing in sewage-contaminated sea-water can, for all practical purposes, be ignored." These latter words with such weight of authority are at present liable greatly to shape policy.—I am, etc.,

Newcastle upon Tyne. G. R. PEBERDY.

SIR,—There is very little direct evidence to show that disease can be spread by sewage pollution of the sea. Those who say that this is because sewage pollution does not spread disease are entitled to express their point of view, but it must not be forgotten that lack of evidence may be due to the difficulty of gathering it. In most outbreaks of infectious disease those who might have been infected via sewage in the sea have been exposed to infection from other and more common sources, and there is no way of distinguishing the one type of infection from the other.

Your readers may be interested in the following brief account of an outbreak of typhoid fever which started in this area in 1952 and which had some exceptional features.

On August 18, 1952, a patient was admitted to the infectious diseases unit of Myland Hospital, Colchester, under my care, suffering from what appeared to be typhoid fever. As she lived with a woman who had suffered from typhoid the previous year we suspected that the original patient had become an undetected carrier. When, however, typhoid bacilli were isolated from the new patient's stools, phage-typing showed them to belong to an untypable strain, quite different from that of her housemate and, in fact, new to this country. Almost simultaneously we admitted a second patient whose stools also yielded the same untypable strain.

Questioning showed one common factor in the diet of the two patients. Both had, at the appropriate time, eaten cockles which they had themselves dug at West Mersea. One of my colleagues dug some cockles from the place which the patients indicated and sent them for laboratory investigation ; the cockles contained the same organism (which has since been christened the "West Mersea" strain). The cockle beds were fairly near the sewer outfall, and further investigations isolated the organism from sewage at the outfall. Attempts were made to trace the infection back through the sewers, but they failed. An intensive search for old cases and carriers on Mersea Island also failed.

Several further cases occurred in this neighbourhood, all showing the same strain of bacillus, and other cases were disclosed in persons living in Watford and Hendon who had been spending their holidays in West Mersea. Of a total of eleven cases infected with this strain ten had eaten cockles and the eleventh had bathed near the sewer outfall—a boy of 11 who had been demonstrating his prowess in swimming under water.

Though it was possible that the carrier was a holiday visitor who might have gone home, warning notices were posted advising the public not to gather shellfish from the beach. Sporadic cases, however, all showing the same strain of bacillus, occurred during the two following years. Shellfish again were involved and it was clear both that warning notices have little effect on the British public and that the

carrier was a permanent resident. Some of the further cases complicated the plot, since the shell-fish involved were a mile or so from the outfall. Eventually a long, laborious, and elaborate process of taking swabs from sewers and drains—the work of the Chelmsford Public Health Laboratory under the direction of Dr. R. Pilsworth—led to the identification of the carrier. The distant spread was accounted for, in all probability, by the fact that the carrier owned a yacht with a flushing closet, which was moored in the neighbourhood of the West Mersea oyster beds. (In my capacity as honorary physician to the Colchester native oysters, I am happy to say that they escaped unscathed.)

It is impossible to escape the conclusion that this outbreak showed that enteric infection can be spread by sewage contamination and even by bathing in contaminated water. The beach concerned is not a notoriously unsavoury one. To the eye and the nose it gives no offence at all, but only the good fortune that the strain of bacillus involved was not a particularly lethal one prevented tragedies. I would add the footnote that though oysters can be—and in West Mersea now are—subjected to compulsory cleansing, cockle-digging is still a recognized and uncontrolled holiday sport round our coasts. It would seem that not only are warning notices of little value but the cooking to which the amateur subjects his harvest of cockles is not enough to sterilize them. The theory that untreated sewage discharged sufficiently far out at sea is infinitely diluted to the point of harmlessness is, no doubt, sound. It seems, however, that discharge into partly land-locked waters is just not good enough and it may well be that shoals and currents may nullify the value of discharge into apparently open sea.—I am, etc.,

Public Health Department, Colchester. JOHN D. KERSHAW.

Vesicles at Injection Sites

SIR,—The letters from Dr. W. G. Benson (July 2, p. 70) and Dr. E. L. Ellis (July 16, p. 230) are of the greatest interest. Unfortunately the pathology of chicken-pox (and herpes zoster) is still very obscure. I think, however, that as the result of work on ectromelia and allied pock diseases in animals we are entitled to assume that when chicken-pox infection is sustained the virus makes its way to chosen target cells within the body, where it replicates. When replication is complete, presumably in about a fortnight, the cells rupture and virus is discharged into the blood-stream, from which in turn it is excreted into the skin and mucous membranes. Wherever there is hyperaemia of the skin naturally more virus particles will be deposited and consequently more vesicles will appear. Perhaps, too, vesicles will appear in that region earlier than they will in the intact skin. This, of course, is speculation, but it is, I think, the nearest one can get to a rational explanation.

I do not think this is the same mechanism that operates in the arm selectively paralysed following an intramuscular injection during the incubation period of poliomyelitis. Here after all it is the corresponding anterior-horn cell of the lower motor-neurone which is picked out for destruction. Why this should happen is not clear, but it would not be unreasonable to assume that noxious stimuli originating at the site of injection and transmitted through the corresponding sensory nerve keep the motor neurone in a state of tension or irritation, thus inducing biochemical changes which render it more vulnerable to the virus. Certainly a similar mechanism would seem to operate in the case of fatigue, when, as we know, the neurones supplying the affected muscles appear to be especially vulnerable. —I am, etc.,

South Middlesex Hospital, Isleworth. G. E. BREEN.

Unusual Case of Glandular Fever

SIR,—On May 3, 1960, an unmarried woman of 23 came to the surgery with a faint papular rash on her face, trunk, and arms. It did not itch and there were no other signs or symptoms. By May 7 the rash had gone. These two visits to the surgery were the very first on the patient's record card. A month later, on June 8, I was called to see her at her home. She now had a striking and extensive rash all over her body.

The rash was worst over her face, where the papules were confluent, and her face was quite swollen, especially over the butterfly area. Every part of her body was covered with small pink papules like a severe case of rubella. There was a rash on the soft palate, but no sore throat, and there was no other lesion on the buccal mucosa. There were a few shotty lymph nodes down the back of the neck and in the submandibular region, but they were small and painless. While staring at the rather unusual rash, it was noticed that the skin had an icteric tinge. The conjunctivae were quite yellow, the urine was dark, and the stools were pale. An examination of the abdomen revealed no liver enlargement, but two fingerbreadths of spleen were clearly palpable. There was no fever, and the patient felt quite well. She was surprised when I told her that she would have to go to bed for a few days.

She said that she had felt worse the week before the rash had appeared, with pains in her throat and eyes, and heaviness of her limbs. Her symptoms had not been bad enough to keep her off work, and it was only the unsightly nature of the rash which had made her call me in. Two days later the rash was fading, but she was still yellow and the spleen could easily be felt. By June 13 the jaundice had gone and she was allowed up. The diagnosis lay between either rubella or glandular fever, both of which can produce jaundice on occasions. On June 16 a blood sample was taken, and the following day I was notified that the Paul–Bunnell titre level was no less than 1 in 2,560, a figure which confirmed the diagnosis of glandular fever. On June 22 the patient had no signs at all. The spleen was no longer palpable, and she started work on the next day.

This case was considered worthy of record because of the extensive and striking rash, the presence of jaundice, and the surprising lack of constitutional symptoms. Did the rash which appeared early in May have any connexion with the fever?

I would like to record thanks to Dr. N. S. Mair for his help in the diagnosis of this case.

—I am, etc.,

Ibstock, Leics. C. A. H. WATTS.

Giant-cell Pneumonias in Children

SIR,—The discovery of the measles-virus by Enders and Peebles[1] a few years ago, and the finding of giant cells in the tissue cultures of measles-virus, revived again the interest in the so-called "giant cell pneumonias" in young children. In your annotation (May 21, p. 1555) you mentioned that I first described the disease 50 years ago.[2] As I am still living I would like to make personally a few explanatory remarks.

Giant cells in pneumonia of children were observed at the end of the last century by several writers as Wygodzinsky,[3] Kromayer,[4] Friedländer,[5] Dürck,[6,7] Honl,[8] and others. I wrote[2] the first monograph and experimental study of the

disease, based on the post-mortem observations of 162 fatal children pneumonias. I was then working as pathologist in one of the largest Continental hospitals for infectious diseases, the Emperor Franz Joseph Hospital in Vienna, with about 2,000 beds. I found giant cells histologically in 27 cases, mostly after measles (20 cases), but also after scarlet fever, pertussis, and hilar tuberculosis. The children were between 1 and 2 years of age. No giant cells were found in fatal cases of adults. All these children were debilitated by other diseases, such as rickets, gastro-enteritis, or hilar tuberculosis. The lobular-pneumonic character of the foci gave a typical appearance, resembling the surface of red-brown, polished marble. Bacteriologically we always found pneumococci, combined with *Neisseria catarrhalis, Haemophilus influenzae,* staphylococci, streptococci, *Escherichia coli,* and *Corynebacterium diphtheriae.* Cytologically transition stages could be observed between enlarged alveolar epithelial cells and the enormous giant cells with up to several hundred nuclei.

Experimentally I produced for the first time typical giant-cell pneumonias in rabbits by intratracheal instillations of tracheal washings from fatal cases of measles of children, or by combination of cultures of *N. catarrhalis* or pneumococci with substances which produced mechanically a similar thick fibrinous bronchial exudate such as found in these cases. For this purpose I used solutions of ammonia or of metal salts as silver nitrate or copper sulphate. A few drops instilled with a pipette into the trachea of rabbits resulted after a few days in fatal pneumonia which showed histologically a typical giant-cell pneumonia as in measles-pneumonia.

In view of the pathological, clinical, and experimental observations it seems to be the severe fibrinous bronchiolar exudate produced by such micro-organisms as virus, coccus, or bacillus in debilitated young children, who cannot expectorate well, which leads to the formation of giant cells in the pneumonias. Thus the development of giant cells seems to be a reaction to eliminate and reduce the fibrinous exudate and its micro-organisms. In practice these observations may be of great value by stressing the importance—even in our antibiotic age—of promoting easier expectoration of bronchiolar exudate in debilitated young children with infectious disease and with signs or symptoms of pneumonia.—I am, etc.,

Bradford. V. R. HECHT.

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Acute Rheumatism and Paediatric Beds

SIR,—I read with very great interest the letter on "Acute Rheumatism and Paediatric Beds" by Drs. Victoria Smallpeice and Hugh Ellis (June 25, p. 1952). For more than a year I have been taking swabs of children's throats, and have been astonished to find that the haemolytic streptococci of Lancefield are sulphonamide-resistant.

In view of the recent increase in the number of cases of acute rheumatism, it is highly probable that the initial throat infections were treated with sulphonamides. In my series of cases oral penicillin was given for seven days, and at the end of that period a second swab was taken, which was negative in all cases. In my experience it is impossible to diagnose the haemolytic streptococcal throat by ordinary clinical examination.—I am, etc.,

Sheffield. J. G. COONEY.

Hormone Treatment of Breast Metastases

SIR,—There is some doubt about the validity of the evidence for a natural retardation of breast cancer at the menopause as presented by the Therapeutic Trials Committee of the A.M.A.[1] and reported in your leading article (July 2, p. 41).

In their report the Therapeutic Trials Committee divide the patients into three groups. In one of these (termed B2) the primary tumour was treated before the menopause and the metastases were recognized after the menopause. A comparatively long *average interval* between primary and metastases was noted in the B2 group and was taken to imply a natural retardation of the disease during the menopause. Further consideration, however, will reveal that this group (B2) is bound to be biased in favour of the longer intervals, for the longer intervals are much more likely to straddle the menopause, or any other given point on the time scale of the disease.

If we take some suitable definition of the menopause as a point in time and make some assumptions about the independence of various variables it is possible to recalculate the figures given by the Committee to show average values of the interval between primary and metastases that might have been expected in the various groups if the menopause has *no effect* on the progression of the disease.

Group	Recognition of		Average Interval Prim.-Met.	
	Primary	Metastases	Reported yrs. mths.	Calculated yrs. mths.
B1	Premen	Premen	2 7	2 7
B2	,,	Postmen	7 3	6 7
B3	Postmen	,,	3 3	3 6

The Committee are not clear as to their definition of the menopause, and if it is considered as an interval rather than point in time this will tend to increase the expected average in the B2 group still further. Unfortunately there is some confusion as to the actual size of the B2 group, and Macdonald[2] has apparently reported the identical group of cases with an average interval from primary to metastases of 11 years 8 months.

It is clear that the menopause may delay the progression of the disease; it is an attractive theory, but this report, as presented, does not demonstrate such a startling regression and the probability values appear to be calculated on an incorrect basis.—I am, etc.,

Royal Marsden Hospital, London, S.W.3. G. B. NEWMAN.

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2 Macdonald, I., ibid., 1960, **172**, 1288.

Hypotension in Meprobamate Intoxication

SIR,—In their letter on promazine overdosage (May 14, p. 1507), Drs. W. Hindle and D. Negus state that meprobamate is virtually non-toxic and that no hypotensive effects have been recorded. *Martindale* (1958) suports this view with the comment "Meprobamate has low toxicity." In fact, fatalities have occurred after excessive ingestion of meprobamate[1] and hypotension has

been recorded after therapeutic amounts[2] and in cases of poisoning with the drug.[3] Bedson[4] described a case of meprobamate intoxication with stupor, in which the systolic pressure fell to 50 mm. Hg, with only transient rise after "coramine" and methylamphetamine. An intravenous infusion of noradrenaline kept the systolic pressure about 100 mm. Hg. Bedson commented on the presence of conspicuous cutaneous vasodilatation and the absence of tachycardia during the period of hypotension. He noted that, in the cases of coma from meprobamate then recorded in the literature, mild, rather than severe, hypotension was usual.

A woman of 34 came under my care in April, 1959, soon after taking 22 tablets (8.8 g.) of meprobamate. Attempts to recover the drug from the stomach were unsuccessful. She was deeply unconscious and notably flushed. Pulse was 78 and of low volume; breathing was slow and shallow. The limbs were flaccid; tendon reflexes and plantar responses could not be elicited. Persistent arterial hypotension (76/60 mm. Hg) was a disturbing feature. There was little response to "mephine" (mephenteramine sulphate) or to "methedrine" (methylamphetamine hydrochloride). The blood-pressure rose to 100/60 mm. Hg soon after noradrenaline infusion was started. The patient regained consciousness 18 hours later. Recovery was uneventful, except that there was some fall in blood-pressure (90/65 mm. Hg) during the three hours after noradrenaline was discontinued. Later readings were normal and no sign of any disease was found. Electrocardiogram done a few days later was normal.

—I am, etc.,

Western District Hospital, Glasgow, C.4. J. D. AITCHISON.

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4 Bedson, H. S., *Lancet*, 1959, **1**, 288.

"Vagosympathectomy"

SIR,—In the *Zentralblatt für Chirurgie* there appears an account of vagosympathectomy in the surgical treatment of duodenal ulcer by Mr. C. Eftimie,[1] of Foscani (Roumania). This operation of vagosympathectomy, designed by Mr. Eftimie, aims, it appears, principally at dividing the vagus nerve fibres in the wall of the stomach by an incision down to the mucosa on both sides of the stomach, anterior and posterior, near to, and parallel to, the lesser curve.

From the account given it would appear that this operation resembles a procedure I commenced in duodenal ulcer cases in April, 1959, as a measure to avoid the side-effects of the routine total vagotomy usually employed. I have called this procedure "intramural vagotomy," but quite appreciate that the descriptive term of "vagosympathectomy" given by Mr. Eftimie is more accurate.

In the cases I have done since April, 1959, the results have been very satisfactory and the gastric acidity has remained within normal limits compared to the high levels pre-operatively. So far as I can ascertain there has been no report of research on vagal regeneration in the stomach wall, but as this event is likely I have endeavoured to prevent it occurring by the addition of a barrier cream containing 50% silicone to the incisions in the stomach wall before sewing them up. Follow-up of the cases I have done does not indicate any adverse effects of the intra-mural vagotomy and the addition of silicone. Whereas the procedure does appear to avoid gastric stasis and chronic diarrhoea.

I hope to publish a full account of this procedure at a later date.—I am, etc.,

The Memorial Hospital, Peterborough. D. W. BRACEY.

REFERENCE

1 Eftimei, C., *Zbl. Chir.*, 1959, **84**, 1414.

Traction Alopecia

SIR,—I was most interested to read Professor H. V. Morgan's observations (July 9, p. 115) on traction alopecia in Sudanese.

I have met with the same condition in West Indians and West Africans in this country, both children and adults. I have noticed that tight plaiting—mentioned by Professor Morgan—is not uncommon amongst negro children in this country, although the coiffure may follow a different pattern and therefore give rise to alopecia at different sites from those seen in the Sudan. Frontal alopecia is not uncommon amongst adult women, due to the effects of vigorous over-brushing and hair straightening. It should be well known that some West African and West Indian women use cold permanent waving to take the curl out of their hair, and this, of course, may damage the hair—particularly if it is fine and woolly. I have also seen subtotal alopecia in a West Indian male, following injudicious use of keratolytic agents in an attempt to produce straight hair. Treatment is simple and involves the abandonment of the hair style and/or cold permanent waving.—I am, etc.,

Guy's Hospital, London, S.E.1. E. J. MOYNAHAN.

Addiction to Hypnotics

SIR,—I was most interested in the concept of "neurotic drug-dependent personality" used by Dr. I. Pierce James in his letter (May 14, p. 1504). This would seem to be a rather *ex post facto* assessment—that is, the assessment is made when there is ample evidence that the patient is "neurotic" (whatever that may mean) and admits he is, or is known to be, addicted or habituated to a drug or drugs. However, Dr. James goes on to speak of "potentially drug-dependent personalities." Is there any evidence that such a specific personality exists? And, if it does exist, by what criteria is it recognized, particularly in the early stage before the indulgence in the drug or drugs has given the game away?

Noyes[1] speaks of three main groups of drug addicts (those with personality problems; those "frankly neurotic"; and those, a less certain group, who have been exposed to drugs during a physical illness but who have continued taking them), and one would be interested to know whether all these groups have a feature in common. Further, whether all the persons taking drugs in this day and age with some degree of dependence (including tobacco and ethyl alcohol) have some special personality factor or personality profile.—I am, etc.,

Heidelberg, Victoria. ALLEN A. BARTHOLOMEW.

REFERENCE

1 Noyes, A. P., *Modern Clinical Psychiatry*, 1953, 4th ed., p. 513. W. B. Saunders Co.

Addiction to Alcohol

SIR,—Dr. Alex J. Macleod's letter (June 25, p. 1953) raises some important questions. On the one hand it is certain that there is a need for at least a limited number of alcoholic treatment centres as advocated in your recent leading article (January 9, p. 117), even though at present alcoholics are under "no obligation . . . to enter or to remain in any centre." This is shown, for example, by the experience at Warlingham Park Hospital, where there has been no dearth of applicants for admission to the alcoholic unit since its establishment and where very few patients discharged themselves prematurely. It can be expected that, with better education of the medical and the lay public about alcoholism, the need for special alcoholic units and out-patient clinics will increase. Their almost total absence in this country contrasts with the presence of a greater or smaller number of alcoholic "consultative bureaux" even in such small countries as the Netherlands[1] and Austria.[2]

However, for every one alcoholic who at present can be persuaded to undergo treatment there must be—as rightly implied in Dr. Macleod's letter—many more who are allowed unhindered to ruin themselves and their families. Nothing can be done for such people until they develop definite physical or mental complications, until they attempt suicide, or until they come into open conflict with the law. These are all events that may not take place until after many years of uncontrolled drinking. Every doctor known to be interested in alcoholics must be familiar with the pathetic requests for help by alcoholics' wives or mothers, who are themselves at the end of their tether: "I am desperate and afraid of what will happen next. I am a bundle of nerves trying to cope with him." Because of this state of affairs the controversial question of legally compulsive treatment for certain alcohol addicts who themselves are not willing to ask for treatment was raised in these columns already several years ago.[3] Compulsive measures in certain cases of alcohol addiction are, for example, in force in the Netherlands[4] and in Sweden.[5,6] Under such circumstances many patients who accept treatment unwillingly change their attitude after a few weeks of enforced sobriety.[6]

The commonly held view that only alcoholics who come "voluntarily" for treatment can benefit is open to serious doubt. At Warlingham Park Hospital and at St. Bernard's Hospital, among alcoholics co-operating well in treatment were quite a few who came from observation wards or were admitted under a court order with condition of residence. Moreover, though in fact technically "voluntary," most alcoholics entering Warlingham Park Hospital arrived there only under the imminent threat of losing wives or jobs and had, to start with, no notion whatsoever of giving up drink. The alcoholic patient whose persistent complaints about not getting any treatment for his condition at Warlingham Park Hospital stimulated the establishment of the first alcoholic group there eight years ago was a man who was "forced" to have residential treatment by the threat of the co-directors of his firm that he would be thrown out unless he entered hospital and stayed there for six months. Though full of resentment and completely lacking in insight to start with, he improved greatly, maintaining complete sobriety after his discharge, until his death from cancer six years later. If there existed a greater number of special clinics and units, the use of a condition of attendance or of residence for certain alcoholic offenders might hold out more hope for some measure of success than generally assumed.

Dr. Macleod rightly stresses the need for prevention and he also mentions the problem of the drunken driver. Of course the great majority of drivers who are repeatedly drunk at the wheel are probably not alcoholics. On the other hand, it may be of some interest here to note the finding of a recent American study that alcoholics were more frequently involved (to a significant degree) in accidents and convicted of drunken or impaired driving than the general population.[7] Of alcoholics seen at Warlingham Park Hospital 23% of the men and 12% of the women admitted having got into trouble through driving when drunk (many more stating that it was only "luck" that had saved them from a similar fate). This happened first at an average age of 32 (men) and 43 (women) years respectively—that is, quite a few years before they first came under medical attention for definite evidence of "alcoholism."

Just as in court, a "hidden" alcoholic may possibly be detected relatively early in his career among individuals with much unexplained absenteeism or falling off in efficiency in their work, and where there is obscure indisposition among members of occupational groups with a relatively high standard mortality rate from liver cirrhosis, such as publicans and their wives, barmen, brokers, showmen, authors, journalists, and merchant seamen,[8] perhaps even among those who have at their disposal a high expense account. By keeping this possibility in mind the G.P. may not infrequently be in a position to spot the early alcoholic and thus contribute to the all-important task of prevention of firmly established addiction.—I am, etc.,

St. Bernard's Hospital,
Southall, Middlesex. M. M. GLATT.

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Reaction after Saccharated Iron

SIR,—Dr. J. A. Daff (July 9, p. 147) relates his experiences of two patients who reacted to second and third injections of "ferrivenin" (saccharated iron oxide). He does not state how these injections were being given. I well remember some years ago giving a first intravenous injection of this substance to a lady in her early 60s in the presence of her husband. When about half the quantity had been injected she had a violent convulsion and was unconscious for about five minutes, with understandable alarm to all present. Incidentally, she had never had a fit in her life before, and she ultimately was none the worse for this particular experience.

I took the matter up with the representative of the firm which manufactures this preparation, and was informed that reactions had been known to occur on occasion. My experience made me revert to oral iron therapy until the advent of the intramuscular preparation "imferon" (iron-dextran) complex. This I found entirely satisfactory and was given repeatedly without incident for some years until it recently became suspect for other reasons.—I am, etc.,

Worleston, Cheshire. JOHN R. T. TURNER.

Mental Health Tribunals

SIR,—Dr. Myrtle M. Hutchins suggests (July 16, p. 233) that I am out of touch with contemporary psychiatry. I trust that I am, but these cases (June 18, p. 1888) came before the courts in 1957, 1958 (two cases), and January, 1960, so I do not think that I can be so very far out of touch.

Regarding her second paragraph, I am not so much concerned with admissions as with discharges. If judges

and juries can find that people have been unjustifiably detained then perhaps general practitioners might also be capable of doing so. I do agree that this is a losing hazard and that when all patients have outgrown the Education Act of 1944 such detentions are unlikely to occur, but until then how many are there who have not been able to escape?—I am, etc.,

F. E. GRAHAM-BONNALIE.

Topsham, Near Exeter.

Child Psychiatry and the Family Doctor

SIR,—In the Annual Meeting Report, Sections of Child Health, General Practice, and Psychiatry (July 9, p. 134), Dr. Gerald Garmany is stated to have emphasized that "the psychiatry of childhood was a part of medicine not education." The psychiatry of childhood is indeed a vital part of medicine as well as of education. Furthermore, the psychopathology of school-group behaviourism is intimately linked with the psychopathology of adult crowd behaviourism and political feeling. Thus politicians with "crowd" hatreds are essentially overgrown schoolboys with "school" hatreds. It is a mere matter of time and opportunity for "school" hatred to enlarge into "crowd" hatred and xenophobia.

The recognition of the historical psychopath (who combines the emotions of a school psychopath with a universal mind) thus becomes an infinitely more crucial finding than the detection, say, of a paratyphoid carrier. It is here that modern medicine is failing lamentably because of its own inability to face social reality. It is here also that the dangers of a xenophobe releasing "school" hatred and "crowd" hatred link up with the need for social amelioration at the school age level.

A child from the ages of 5 to 15 spends 29,000 waking hours in the home and 13,000 hours in the school classes. The parents and the teachers thus play an immeasurably more important factor in the child's spiritual growth than the odd hour or two that the school doctor, family doctor, or child psychiatrist can offer as a placebo. There is thus scope for far more careers in school psychiatry, but the whole "closed shop" of modern psychiatry offers no outlet at all for those interested in social psychiatry as opposed to individual psychiatry.—I am, etc.,

Penn, Wolverhampton. GARETH R. DAVIES.

Crime and Sin

SIR,—In your report of Sir John Wolfenden's "Winchester Address" (July 9, p. 140) Sir John asks the question, "But if you looked at the Ten Commandments dispassionately, how many were embodied in the law of the country?" Your interested readers might like to know of the following remarkable passage in Sir James Fitzjames Stephen's *History of the Criminal Law of England* (1883):

"The criminal law may be described with truth as an expansion of the second table of the Ten Commandments. The statement in the Catechism of the positive duties of man to man corresponds step by step with the prohibitions of a criminal code. Those who honour and obey the King will not commit high treason or other political offences. Those who honour and obey in their due order and degree those who are put in authority under the King will not attempt to pervert the course of justice, nor will they disobey lawful commands, or violate the provisions of acts of parliament, or be guilty of corrupt practices with regard to public officers or in the discharge of powers confided to them by law.

"Those who hurt nobody by word will not commit libel or threaten injury to person, property, or reputation, nor will they lie in courts of justice or elsewhere, but will keep their tongues from evil-speaking, lying and slandering. Those who hurt nobody by deed will not commit murder or administer poison, wound, or assault others, or burn their houses, or maliciously injure their property.

"Those who keep their hands from picking and stealing will commit neither thefts, nor fraudulent breaches of trust, nor forgery, nor will they pass bad money. Those who keep their bodies in temperance, soberness, and chastity, will not only not commit rape and other offences even more abominable, but will avoid the causes which lead to the commission of nearly all crimes.

"Those who learn and labour truly to get their own living will not be disorderly persons, cheats, imposters, rogues, or vagabonds, and will at all events have taken a long step towards doing their duty in the state of life to which it has pleased God to call them."

The clergyman who said "the root of all morality and the root of all law was to be found in the Ten Commandments" was right in the sense that every human situation has a theological interpretation. Hence, William Temple's apt words, "Very few citizens are so established in virtue as to be able to dispense with the support of the law and its penalties without moral deterioration."—I am, etc.,

Harrogate, Yorks. JOHN PEACOCK.

Is Trichomonal Infestation Venereal?

SIR,—Drs. R. D. Catterall and C. S. Nicol (April 16, p. 1177) report finding the organism in all the female contacts of 56 males suffering from *Trichomonas vaginalis* urethritis, and Dr. L. Watt (May 14, p. 1502) obtained 18 positive cultures from the husbands of 30 wives attending for treatment of vaginitis due to the same cause. These results appear, at first sight, to justify the former authors in concluding that *T. vaginalis* infestation is spread in the great majority of cases by sexual contact, and, therefore, should be classed as a venereal disease. However, the case is not so easily decided, as, although the finding of *T. vaginalis* is definite proof of a sexual origin in the case of the male, it must not be assumed that the same conclusion holds good for the female.

I think that it will be admitted that *T. vaginalis* infestation in the female is a relatively common disorder, whilst *T. vaginalis* urethritis in the male is relatively rare, and I cannot see how this variation in the frequency between the sexes can be explained on a venereal basis. In my opinion this can only be explained on two assumptions: either (1) *T. vaginalis* fails in the great majority of cases to bring about any pathological reaction in the exposed male, or (2) that, when *T. vaginalis* is discovered in *any* condition, it is grafted on some other infection which allows for its growth—i.e., simple parasitism. If one of these two explanations were not correct, then not only would all married men whose wives harbour *T. vaginalis* suffer from urethritis, but the condition would already have become so common as to outstrip gonorrhoea in frequency in those attending our clinics, especially as to date no really satisfactory treatment for either sex has been devised and continence in the presence of this infestation has not been preached as in the case of gonorrhoea. The full implication of this fact—i.e., variation in frequency between the sexes, will not be pursued here, as I do not wish to prolong this letter unduly.

It may be asked how to explain the findings of Drs. Catterall and Nicol on the one hand and those of Dr. Watt on the other. Those of Drs. Catterall and Nicol are not difficult to explain, since, given the fact that *T. vaginalis* is a parasite and that the male consort had active urethritis in which the organism was present, it appears to me that it

would be a source of astonishment if the organisms were *not* recovered from the female consort. Does not coital contamination rather than infection explain readily the results of this investigation? Turning to the findings of Dr. Watt, may one ask how many of the husbands with positive cultures were suffering from *T. vaginalis* urethritis at the time of examination? May I anticipate his answer by saying that I believe none, or at most a very small proportion, showed pathological reaction to the organism? Here again coital contamination suffices to explain the positive cultures, and Dr. Watt must have sensed the difficulty as he examined 50 males attending his clinic and recovered the organism in only eight. It would be interesting to find out how many of these eight had active *T. vaginalis* infection, or were they merely attending for other conditions?

From what has been said above much additional information is needed before we can profitably discuss the origin and spread of conditions in which *T. vaginalis* is found, but an investigation on a large scale similar to that undertaken by Dr. Watt would give valuable information, especially if on this occasion the question was asked, How many husbands whose wives are known to harbour *T. vaginalis* suffer from *T. vaginalis* urethritis? Whatever be the final answer, let us not take the retrograde step of enlarging the venereal diseases by adding yet another to this archaic category, but rather let us follow the suggestion of Mr. E. E. Philipp and Dr. E. Dunlop (June 18, p. 1889) and coin some such term as "Department for the Investigation and Treatment of Medical Genito-Urinary Disease," as such a term more nearly describes the work already carried out by venerologists to-day. In this way much unnecessary mental suffering associated with the treatment of genito-urinary affections will disappear, and if this happy result follows from the paper by Drs. Catterall and Nicol, then indeed will their investigations have been worth while.—I am, etc.,

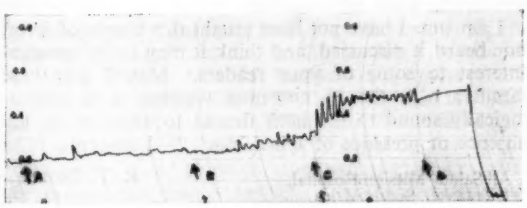
F. L. LYDON.

V.D. Department,
King's College Hospital,
London, S.E.5.

Abortion and Ergometrine

SIR,—In my letter (February 13, p. 497) I urged general practitioners to give ergometrine intravenously to patients who are bleeding from an incomplete abortion. Professor F. J. Browne replied (April 23, p. 1273) that he did not think that ergometrine acted on the uterus early in pregnancy, and referred to a paper by Schild, Fitzpatrick, and Nixon.[1] In this paper it was suggested that oxytocin might be a more useful drug in the treatment of abortion.

Pharmacologically oxytocin and ergometrine have different actions on the uterus. Dr. C. N. Smyth, working in this department, has shown that even early in pregnancy oxytocin stimulates the uterus to act in a co-ordinated way. Provided that the dose is not too large, an oxytocin infusion will produce good contractions each followed by relaxation. Larger doses produce spasm of the uterine muscle. Ergometrine in small doses increases the uterine tone and produces a fast, often irregular, rhythm. A larger dose results in a powerful tonic contraction which is more prolonged than that achieved with oxytocin. Smyth reported these findings at the Symposium on Oxytocin at Montevideo last year (to be published by Pergamon Press).



Further evidence of the action of ergometrine on the uterine muscle early in pregnancy is supplied by the accompanying tracing. A balloon, similar to the one used by Schild *et al.*,[1] was placed as high as possible in the fundus of the uterus at the eleventh week of pregnancy, and contractions recorded by an electromanometer. Fifteen minutes (A to B on tracing) were allowed as a baseline. A weak infusion of ergometrine malleate was then given intravenously at a rate of 0.004 mg. per minute (B to C). This small dose produced feeble, frequent contractions. After an intravenous injection (0.5 mg.) of ergometrine vigorous contractions and uterine spasm developed (C to D). A vaginal hysterotomy was performed, during which the uterus remained well contracted and the blood loss was minimal. —I am, etc.,

J. R. SAUNDERS.

University College Obstetric Hospital,
London, W.C.1.

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Dumping Syndrome

SIR,—Le Quesne, Hobsley, and Hand interpreted the cuffing test[1] on the assumption that after 20 minutes' cuffing the volume of the circulating blood is diminished by the volume of the trapped venous return (15%). This assumption is contrary to what we know of the homoeostatic regulation of the plasma volume.

Thus after massive haemorrhage resulting in 15% reduction in the plasma volume, the reduction was fully compensated in less than 5 minutes in the dog.[2] Reduction may also be corrected by redistribution and shift in the erythrocyte volume: plasma volume ratio.[4] That rapid reduction of the plasma volume by 15% causes, as such, a dramatic reaction is made doubtful by its trivial occurrence, e.g., after a single minute of running[5] or (16%) after 1½ minutes' work on the treadmill.[6] Other sectors of the gut are, it seems, less likely to cause symptoms, e.g., a therapeutic dose of Epsom salts, which retains 400–700 ml. water in the intestine.

In the dumping syndrome, the correlation of symptoms on the one hand, and marked fall in plasma volume, oral hypertonic glucose-"lag" curve, and, now, positive cuffing reaction, on the other, must be accepted as facts. The question I wish to raise is whether the reduced plasma volume hypothesis does account for the facts. Another possible mechanism is suggested by the cuffing response.

"Positive reaction to cuffing consisted in faintness, drowsiness, and sweating, progressing in one case to complete loss of consciousness with disappearance of the radial pulse. . . . In several cases the test had to be suspended." The cuffing reaction may be related to the effect on the vasotonus of anaesthetized rabbits of unifemoral clamping, which was demonstrated in micro-angiographs by Trueta *et al.*[3]: contraction of the contralateral femoral artery and of the arteries of the trunk; dilatation of the mesenteric artery, which gave also a denser shadow and dilated maximally following injection of adrenaline. If the cuffing reaction and the dumping syndrome were instances of splanchnic stimulation, we would have to demonstrate in both the symptom-triad: portal pooling—reduced plasma volume—steep rise in the blood sugar, followed by fall of "lag" type. Splanchnic pooling in the cuffing reaction is suggested by the above experiments. The blood sugar and the plasma volume are not reported on in the cuffing test. Both splanchnic pooling and reduced plasma volume fit with the dumping syndrome and so would the rise in blood sugar—if the increment in the blood proved to be endogenous.

LeQuesne and Hobsley[2] introduced their analysis of the "lag" curve with the statement: "even after gastrectomy the shape of the blood-sugar curve must depend upon the balance between the rate of absorption of glucose from the intestine and the rate of removal from the blood-stream." This is no doubt an oversight, for, irrespective of preceding ingestion of glucose or other nutrients, the following are known to cause the *liver* to release and load the blood with glucose: (1) Claude Bernard's *piqûre*. (2) Splanchnic stimulation.[9] (3) Stimulation of the adrenal medulla.[10] (4) Adrenaline.[12] (5) "Secondary" shock.[16] *In all these cases blood-sugar curves of the "lag" type result.* (6) Glucagon, the curve in this case is normal.[13 14] LeQuesne and Hobsley stipulated early inhibition of the absorption into the blood-stream, while in the above case it would be instant. Actually only repeated testing of the sugar content of the vena portae could differentiate non-absorption of sugar from its being held by the liver.

Concerning the interrelation, glucose and intestinal motility: in 150 radiological studies of the effect of hypertonic glucose on motility a number of patients exhibited dumping and "lag" curves (without gastrectomy), but no marked dilution of the meal; contrary to patients in whom glucose caused peristaltic arrest and the "curve" was flat.[15] Some of the pictures in this group were reminiscent of acute gastric dilatation. Dr. Peter Kerley was the radiologist. A first step to verify if the adreno-sympathetic hypothesis is merely possible or also probable might be to repeat the cuffing tests with contemporaneous plasma volume and blood-sugar curves.—I am, etc.,

London, W.1. T. CSATO.

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Contrecoup Fracture of the Sternum

SIR,—Yesterday another case of "contrecoup" fracture of the sternum presented at my surgery. However, I did not comprehend the mechanism of injury until I read of Dr. James Simpson's case in your issue of May 14 (p. 1505), which arrived in the mail yesterday with its reference to Mr. Miles Fox's memorandum (March 26, p. 935).

On June 13 a tall 14-year-old pre-pubertal boy was riding his bicycle down a steep sandhill when he went over the handlebars, landing on his occiput. His mother kept him at home two days "in case he had concussion" before he returned to school and his morning "paper run" delivery. He was troubled a little by chest pain in the region of and to the right of the sternum only on exertion, especially with his arms, and on laughing. He played in a football match on June 19, during which he was "grabbed" over the sternum. The pain became worse during the match and persisted, but he did not seek medical advice until June 23. Examination showed tenderness about one inch below the sternal angle, but "springing" the sternum throughout its length caused acute pain. Springing, however, risks damage to structures behind the sternum from bone spicules. He asked me to examine his occiput, but there was no evidence of injury there.

X-ray examination confirmed an isolated fracture of the superior segment of the gladiolus without displacement. It was actually a "greenstick" fracture concave anteriorly. The cartilage between the first and second segments of the gladiolus has not ossified. He is being treated by rest in bed at home.

The mechanism of this fracture was apparently acute anteflexion of the cervico-dorsal spine as described in the other two cases, although the evidence in my case is not so convincing. The absence of the typical posterior displacement of the upper fragment in my case may be attributed to his youth. Of interest is the fact that this physically active boy continued his normal routine after fracturing his sternum for 10 days before seeking medical attention. Perhaps this fracture is more common than is generally believed. My patient thought he had fractured ribs, and it would not be difficult for a first-aid or medical attendant to make this error.—I am, etc.,

Bendigo, Victoria, Australia. LLOYD K. MORGAN.

Needle and Thread

SIR,—I visited an elderly patient this morning who recently had an ovarian cyst removed. While talking to her, she asked me to have a look at a painful area in her right thigh, which had troubled her for several months. Lately a black spot had appeared and she had mentioned it while in hospital. The house-surgeon had told her it was a filiform wart; the night sister had said it looked like a needle, and that she could have threaded it.

It was treated with a dressing in hospital, which made it smaller and more comfortable. To-day there was a black object projecting about one-eighth of an inch from the skin surface at the lower end of the right femoral triangle. It pulled out easily with forceps and was indeed a household sewing needle one and three-eighths inches long. It had lost its metallic shine and was a dull black. My patient had no idea how the needle had got into her body.—I am, etc.,

Dorchester on Thames, Oxford. A. P. MILLAR.

C.S.F. Manometry

SIR,—I believe it is widely taught that, in performing lumbar puncture, the head and neck of the patient, as well as the back, should be flexed; and I think that in practice this is often done quite forcefully. I have noticed that, if the head is released, C.S.F. pressure falls considerably, and I do not now read the pressure until the head has been released. Conversely, it seems to me to be less disconcerting to patients, and less provoking to those who are irritable, to flex the neck rather than grasp it, as is usually done in Queckenstedt's test, to obtain the same information.

I am sure I have not been taught this source of error, nor heard it discussed, and think it may be of practical interest to some of your readers. May I ask those familiar with the phenomenon whether it is physiologically sound to use neck flexion to demonstrate the absence or presence of spinal block?—I am, etc.,

All Saints' Mission Hospital, Transkei, South Africa. R. F. INGLE.

Static Electricity from Curtain Rails

SIR,—During the recent dry weather sparks have been noticed when moving bedside curtains which were hung from non-metallic rails. On reflection it is no surprise that friction between two insulators (when dry) will set up an electrostatic charge.

Several types of these rails and fittings have been produced in the past few years and, since they are so free running and silent, they have been adopted in many hospitals for bedside curtains. The usual practice is to secure them to a framework—often metallic—which is not separately earthed. (A formidable task for every bed in every ward in all the hospitals concerned.) One is worried when one thinks that ether may have been used on a patient in the enclosed space of the curtained cubicle and that there is the possibility of a static discharge when the curtains are opened at the completion of the procedure. I doubt if a serious danger in fact exists, but it would be most alarming if some patient or nurse should have to show us what the extent of the danger might be.—I am, etc.,

Stanmore, Middlesex. A. W. WARLTIER.

Suxamethonium Muscle Pains

SIR,—With reference to the numerous discussions concerning muscle pains after suxamethonium which have appeared in your journal, I would like to make one observation. This is that in my experience when suxamethonium chloride is used in conjunction with electroplexy it never gives rise to subsequent muscle pain.—I am, etc.,

Paignton. R. J. T. WOODLAND.

Translating from Russian

SIR,—Following Professor D. H. Smyth's lead (May 21, p. 1561), your correspondents (July 2, p. 71) have been calling for the publication of a Russian-English dictionary which should be absolutely comprehensive, should include genders, stress marks, etc., and should be printed in clear type. Surely such a dictionary, if it could be produced, would be uncomfortably large and prohibitively expensive, in view of the extremely limited demand. Furthermore, the publication of the dictionary would be a prolonged business, and many new terms would have been added to the vocabulary by the time it was eventually printed, making it necessary to take steps to keep it up to date, and detracting from its assumed value as a complete work of reference.

I should like to make the following suggestions. Firstly, it must be recognized that the translation of scientific Russian texts is a specialized job, requiring specialized knowledge and qualifications, one of which is the acquisition of an extensive vocabulary from familiarity with Russian scientific literature on subjects with which the translator is also familiar. Secondly, the existing facilities, both for scientific translation of the occasional article and for cover-to-cover translation and abstraction of current Russian medical and scientific journals, should be more widely publicized. Thirdly, one of the organizations, in this country or abroad, handling Russian scientific translation on a large scale should be encouraged to maintain a "living" dictionary in the shape of a reference bureau, to which requests for information on terms not included in the existing dictionaries could be made. Such an arrangement would be far cheaper than a new dictionary, and would have the advantage of being absolutely up to date all the time. It would also serve as a focal point where many experienced translators could pool their ideas and share their knowledge, to the great ultimate gain of all who are engaged on this work. An additional advantage of the idea would be that, if the demand for the "super-dictionary" grew, the bureau would be in an ideal position for composing it.—I am, etc.,

Rotherham, Yorks. BASIL HAIGH.

Fools and Wise Men

SIR,—In the concluding paragraph of his Centennial Oration of the Institute of Neurology Dr. Macdonald Critchley (July 2, p. 6) has attributed to Lenin a modified version of a well-known Sanskrit saying which means: "All the wise men may not be able to answer even a single question asked by a fool; for he who appears or pretends to be a fool may even be wiser than the wise men."

However, English readers may be interested to know that in 1806–7 some students compiled a list of questions and went in a deputation to the then President of the Royal Society (Sir Joseph Banks) with a request that they be allowed to circulate copies of the list. The despotic Sir Joseph angrily dismissed the deputation, remarking at the same time that "a few fools could ask more questions in half an hour than wise men might answer in years." This anecdote has been mentioned in the preface to the first volume of the *Transactions of the Geological Society*, published in 1811. Sir Francis Galton, F.R.S., has vouched for its authenticity in page 9 of the October number of the *Biometrica* published in 1901, pointing out that one of the deputationists, Mr. Greenough, later became an F.R.S.—I am, etc.,

MANGALORE NARASHIMA PAI.

Belmont Hospital Neurosis Centre, Belmont.

Vacuum Cleaner Injury

SIR,—In reference to the medical memorandum by Mr. Miles Fox and Dr. E. L. Barrett (June 25, p. 1942), I wonder if the vacuum cleaner injury which they described is really as uncommon, or as unknown, as most of us would like to believe. Perhaps you and others may remember the bawdy parody of Shakespeare's "Five Ages of Man" in which the last stage of all is represented by "vodka and vacuum cleaners."

After reading this memorandum I quoted this now rather ancient parody to some of my staff, and a Polish graduate of a well-known university said: "You have that in your country too. We had it also in an exact translation in my country when I was a medical student." Needless to say the delicacy and decorum of your paper forbid a recitation of the original.—I am, etc.,

Lanark. J. BRYANT.

Blue Cross and Blue Shield

SIR,—I wish to call to your attention an error in the article by Dr. J. O. F. Davies entitled "Visit to the U.S.A." (June 18, p. 1879). Blue Cross is said to pay doctor fees and Blue Shield to pay hospital expense in the article. This is just reversed. It is Blue Cross that pays the hospital expense and Blue Shield pays the doctor's fees.—I am, etc.,

Massachusetts General Hospital, Boston, U.S.A. M. L. JANOWER.

Obituary

WILLIAM MORTON, M.D.

Dr. William Morton, consulting physician to the City and Sherwood Hospitals, Nottingham, died on July 9. He was 52 years of age.

William Morton was educated at Glasgow High School and Glasgow University. He graduated M.B., Ch.B. in 1930, and proceeded M.D. with commendation in 1936. After qualification he became house-surgeon at the Royal Hospital for Sick Children, Glasgow, and he was then appointed resident medical officer to the Withington Hospital, Manchester. He became medical superintendent of this hospital in August, 1939, just as the second world war broke out. During the war he served at home and overseas in the R.A.M.C. and attained the rank of Lieutenant-Colonel in charge of the medical division of Chester Military Hospital. In 1946 he was appointed medical superintendent of the City Hospital, Nottingham, and when the Health Service began he became consultant physician to the City and Sherwood Hospitals. He took an active part in old people's welfare and was chairman of the East Midlands Old People's Welfare Committee at the time of his death. He was a founder member of the Medical Society for the Care of the Elderly (now the British Geriatric Society), and was chairman of its executive committee from 1953 to 1956, and treasurer from 1954 to 1956. He was president of the Sheffield Regional Group of Occupational Therapists and treasurer of the Nottingham Medico-Chirurgical Society. He also served on many other committees, including the Sheffield Regional Hospital Board Geriatric Advisory Committee and Committee on Rehabilitation.

During his time in Nottingham Dr. Morton was closely concerned with the completion of many new developments in the City Hospital, including a theatre block and out-patient and *x*-ray departments. He also established an active occupational therapy department which had one of the first rehabilitation kitchens in the country. In the days when a geriatric unit was something of a novelty he adapted two wards in the City Hospital to serve as a treatment and assessment unit, long-stay accommodation being provided in the nearby Sherwood Hospital. He described this unit in an article in the *British Medical Journal* in 1952. He also arranged a "holiday service" by which relatives could be relieved of the care of their sick old folks for a holiday spell. These arrangements have set a pattern which has been widely followed.

His appointment as medical superintendent of the City Hospital lost its administrative responsibilities when the Health Service began, but with the nominal title of physician superintendent he retained the best of the personal functions of such an office. He took more than his share of committee work, particularly in relation to planning, and became a valued friend and adviser of his medical colleagues and a host of others in and outside the hospital service. His manner was quiet and occasionally abrupt, and he had a remarkably successful way of getting things done. As a clinician he was wise and knowledgeable. He was convinced of the nature and extent of his final illness long before the details were clinically detectable by others. He faced up to the pain and inevitability of its course with the courage that all his friends expected.

His death makes a gap which it will take long to fill. He leaves a widow and three children of school age.—J. M. M.

D. A. D. KENNEDY, *M.C.*, M.B., Ch.B., M.R.C.O.G.

Dr. D. A. D. Kennedy died in the Cambridge Military Hospital, Aldershot, on June 23, after a short illness. He was 69 years of age.

David Anderson Duncan Kennedy, a Dundonian, was born in France. He was educated at Morrison's Academy, Crieff, and went on to study medicine at St. Andrew's University, where he graduated M.B., Ch.B. in 1913. He served in France during the whole of the first world war and was awarded the Military Cross. On demobilization he held first an obstetric house appointment at the Royal Free Hospital, London, and then became registrar at the Samaritan Hospital. After a period of private practice he was appointed, in 1933, professor of gynaecology and obstetrics in the University of Bagdad. He relinquished this appointment in 1937 and resumed private practice in London. In 1939 he rejoined the R.A.M.C., and after a short spell at Catterick was posted to the Louise Margaret Military Families Hospital, Aldershot, as specialist in gynaecology and obstetrics, with the rank of major. He remained in this appointment until 1948, when he became director of the Aldershot Maternity Unit. He retired in 1955.

T. P. B. writes: D. A. D. Kennedy was a well known figure in Aldershot and Fleet. On first encounter he appeared a shortish, powerfully built, and rather dour Scot, but his patients soon discovered how gentle were his strong hands and what understanding and sympathy underlay the apparent gruffness. We, his colleagues, will remember him for his loyal friendship, his diagnostic insight, and his professional skill. Others will remember him as a gifted gardener, and some as an enthusiastic fisherman. We all remember him, with gratitude, as a much-beloved person.

In 1925 he married Dr. Agnes Thomas, now a consultant anaesthetist in London. To her and to their daughter, Dr. Margaret Campbell, we extend our deep sympathy.

A. C. STRAIN, M.D.

Dr. A. C. Strain, who practised for many years in West Hartlepool, died in Edinburgh on June 21, after a long and at times painful illness. He was 78 years of age.

Arthur Charles Strain was born in Blairgowrie on January 12, 1882, and received his early education at Dundee and his medical education at Edinburgh University, where he graduated M.B., Ch.B. in 1904 and proceeded to the degree of M.D., with honours, in 1907. After holding appointments in Edinburgh, he joined the late Dr. Angus MacGregor, a well-known general-practitioner-surgeon in West Hartlepool, as assistant, becoming his partner not long afterwards. On the retirement of Dr. MacGregor he was joined in partnership by his nephew, Dr. George Strain.

At an early stage of his professional career he was appointed to the staff of the Cameron Hospital as assistant surgeon and soon rose to the position of full surgeon, a post he filled with dignity and devotion. On the advent of the National Health Service he retired from the staff. He continued in general practice until a cerebral accident three years ago caused partial blindness and compelled him to give up all his professional work. From that time his health gradually deteriorated, although he was able to join his friends in some small social activities from time to time.

During his career he was acknowledged by his colleagues to be a good obstetrician and gynaecologist whose opinion was always sound. Chairman of the West Hartlepool Division of the B.M.A. in 1922, he was for many years a J.P. of the county borough. In the first world war he served in East Africa in the R.A.M.C.

Dr. Strain's death removes one more link with the past generation of family doctors and general-practitioner-surgeons. He was an ideal family doctor, invariably kind, helpful, and courteous to colleagues and patients, and many there were who regretted his retirement. He had a reserved but genial personality and one of the writer's almost daily pleasures was to have a chat with him on current medical affairs. He was a staunch Presbyterian and the teachings and discipline of the "Auld Kirk" had a great influence on his life.

The last months of his life were darkened by the death of his wife. He leaves two married daughters.—J. E. M.

MAURICE DWYER, *M.C.*, M.R.C.S., L.R.C.P.

Dr. M. Dwyer died in retirement on June 24 after being in rather poor health for the past few years. He was 72 years of age.

Maurice Dwyer was born in Dewsbury in 1888. He decided not to follow his father into the legal profession and chose medicine, studying first at Leeds, under Moynihan, and then at St. Thomas's Hospital, London, where he qualified in 1916. He at once joined the R.A.M.C. Supplementary Reserve, and with the rank of captain saw active service in Mesopotamia and the North-West Frontier of India. During the Middle East campaign he was awarded the Military Cross. After the war he was house physician at Stafford Infirmary for a few months and then went into general practice in Tattenhall, Cheshire, where for 35 years he was a family doctor in the truest sense of the word. He was a member of the B.M.A. and was chairman of the Chester Division from 1938 to 1942. He took part in many activities in his village. At one time he was chairman of the local branch of the British Legion, an organization which was close to his heart. He was also keenly interested in sport. He retired to Grange-over-Sands nearly five years ago. He is survived by his wife.

K. C. K. writes: Dwyer will be remembered most of all for his humanity. He understood human nature and its foibles, and it was this faculty which made him a good doctor. In addition, his wisdom was sure and his judgment sound. He will also be remembered for his tall and commanding figure; yet withal he had a gentle disposition. In public, and while attending meetings, his tendency was to say as little as possible. On the other hand he loved to be in good company and was an excellent raconteur.

E. F. ROUTLEY, M.D., M.S., F.R.C.S.(C.)

We record with deep regret the death of Dr. E. F. Routley at Long Beach, California, on May 25. He was 40 years of age. He was the only son of Dr. T. Clarence Routley, of Toronto, and his wife Florence, who made many friends on this side of the Atlantic when Dr. Routley was President of both the Canadian and British Medical Associations in 1955–6, and before that when he was General Secretary of the Canadian Medical Association.

Eric Routley was educated at Upper Canada College and the University of Toronto. He graduated M.D. in 1943, when he was silver medallist in his class. After internship at the Toronto General Hospital he served in the R.C.A.M.C. until 1946, when he started on six years of postgraduate training in surgery at the Mayo Clinic. He gained the M.S. and the M.Sc. (Minnesota), the diploma of the American Board of Surgery, and the F.R.C.S.(C.). He then established himself in practice in Saskatoon and held a teaching and research appointment in the Department of Surgery, University of Saskatchewan. Routley subsequently accepted an invitation to join a group in Dayton, Ohio, and recently moved to Long Beach, California, where he was actively at work until his untimely death.

Dr. Routley is survived by his widow and three children. To them and to his parents will go the sympathy of their friends in this country.

R. F. D. MacGREGOR, C.I.E., *M.C.*, M.B., Ch.B. M.R.C.P.Ed.

Lieutenant-Colonel R. F. D. MacGregor, formerly deputy director-general of the Indian Medical Service, died at Edinburgh on June 22. He was 75 years of age.

Robert Forrester Douglas MacGregor was born at Edinburgh on January 5, 1885, and was educated at George Watson's College and Merchiston Castle School. Entering Edinburgh University as a medical student in 1903, he graduated M.B., Ch.B. in 1908. He was elected a member of the Royal College of Physicians of Edinburgh in 1920. After graduation he held the appointment of assistant medical officer at Stirling District Asylum before entering the Indian Medical Service as a lieutenant in 1910. Promoted captain in 1913, he was on active service in France, Mesopotamia, Palestine, and Syria during the first world war, being awarded the Military Cross in 1916 for his services in Mesopotamia. During the war he was also four times mentioned in dispatches. From brevet rank in 1919 he attained his majority in 1921, promotion to lieutenant-colonel coming eight years later. From 1929 to 1931 he was chief medical officer in Baluchistan, and from 1931 to 1933 held the corresponding post in Central India, and for six years (1933–9) he was residency surgeon in Hyderabad (Deccan). He was appointed C.I.E. in the 1939 Birthday Honours, and later in the same year became deputy director-general of the I.M.S., holding this appointment until 1945. A member of the British Medical Association for over fifty years, he was president of the Hyderabad Branch in 1934–5 and of the Delhi Branch from 1940 to 1943. He leaves a widow.

MARCELL GANG, M.D. (Vienna), M.R.C.S., L.R.C.P.

Dr. Marcell Gang, of Cardiff, died on June 28. He was 68 years of age.

I. G. writes: Marcell Gang was born in Cracow in 1892 and became a naturalized British subject in 1947. He was trained in the Medical School of Vienna at a time when, as the capital city of an empire, the university chairs were occupied by internationally known teachers of medicine who endeavoured to impart not only knowledge to their students but also emphasized in what manner the knowledge should be applied in practice. According to the famous Professor Nothnagel, only good men can be good doctors. Marcell Gang worthily embodied this ideal, and lived up to the admirable precepts of his ancient university. An upright, cultured man of distinguished appearance, with a wide knowledge of medicine, he approached his patients with an inexhaustible fund of kindness and tolerance.

Marcell Gang adorned our profession, and we, his friends and colleagues, will sadly miss him. He has left, however, an indelible impression of his great personality in our hearts. We all feel that it was a great privilege to have known him and to have seen him at work. His devotion to duty and his death in full harness, undeterred by previous warning symptoms, are a shining example to all of us who have always considered him as a model of what a good general practitioner should be. To his widow and sons we extend our profound sympathy in their great bereavement. One of the sons can, fortunately, carry on the good work of his highly respected father.

G. G. MARSHALL, M.B., Ch.B., D.P.H., D.A.

Dr. G. G. Marshall died at his home in Dore, near Sheffield, on June 15. He was 70 years of age.

George Guthrie Marshall was born at Dalkeith, Midlothian, in 1889. He was educated at George Watson's College and Edinburgh University, where he graduated in 1912. After holding an appointment as house-surgeon at the Royal Infirmary, Edinburgh, he came to Sheffield as assistant medical officer at Fir Vale Hospital (now City General Hospital). In August, 1914, at the outbreak of war, he joined the R.A.M.C. and served in France until 1919, when he was demobilized with the rank of major. He returned to his hospital appointment in Sheffield and at the same time he took a course in public health in Sheffield University, gaining the D.P.H. in 1921. In 1923 he settled in practice in Dore and continued in active work up to within a few weeks of his death. He took an interest in anaesthesia and was granted the D.A. in 1939. For some years he held the appointment of anaesthetist at the Royal Infirmary, Sheffield, and when he retired he was appointed honorary consultant anaesthetist.

J. C. writes: George Marshall was held in high esteem both by his patients and his colleagues. He was a kindly

man and never spared himself when sick people required his attention. During his last year he carried on his work suffering great personal discomfort. In his younger days he was a keen rugby player and played regularly for Watsonians, Sheffield Club, and for Yorkshire. In his later years his chief recreation was golf. He will be greatly missed in Dore and Sheffield, and our sympathy goes out to his widow and his two sons, of whom one is a master at Rugby and the other holds a teaching appointment in Australia.

SYDNEY HUNT, M.R.C.S., L.R.C.P.

Dr. Sydney Hunt, of Spondon, near Derby, died on June 19, at a nursing-home at Oxford. He was 85 years of age.

Sydney Hunt was born on November 27, 1875, and was educated at the Merchant Taylors' School and St. Thomas's Hospital. Qualifying in 1900, he obtained the post of house-surgeon at his teaching hospital and then began practice in the village of Spondon, four miles from Derby, where he remained until his death. He was well established in practice when the first Insurance Act was passed, and he took a reasonable view of the problems at that time.

When British Celanese Ltd. opened their works in Spondon he was appointed visiting doctor, and in 1930 he gave up his practice to become whole-time medical officer to that firm. He enjoyed this work, having happy relations with the management and the employees. He retired in 1942. Appointed medical officer of health to the Shardlow area in 1914, he retained this post until 1954.

Hunt was a good doctor, taking much trouble over his more difficult cases. He was respected by the local consultants as a man with the best type of family practice. There are many people in Spondon who remember him affectionately as their doctor. A very regular attendant of the Derby Medical Society, he was president in 1929. He was also a firm supporter of the British Medical Association, being chairman of the Derby Division in 1923–4. During all his years in Spondon he was president of the local cricket club.

Dr. Hunt leaves a widow, three sons, one of whom is a doctor, and a daughter.—H. B.

Sir ERNEST ROCK CARLING, LL.D., M.B. F.R.C.P., F.R.C.S., F.F.R.

The obituary of Sir Ernest Rock Carling was published in the *Journal* of July 23 (p. 313).

F. H. K. G. writes: It was my privilege to serve as secretary of the Medical Research Council's War Wounds Committee and of its Burns Subcommittee throughout the period of Sir Ernest's chairmanship of both bodies, from June, 1944, until they were disbanded after the end of the second world war. Our association on the Burns Subcommittee was, indeed, of still longer duration, for he had been its chairman and I its secretary from the date of its inception at the time of the blitzkrieg in 1940. No man—and no committee—ever had a more stimulating, eager, hard-working, knowledgeable, yet withal kindly and modest chairman. He handled large committees of experts of very different views with consummate tact and skill and I never saw him ruffled or impatient. Always anxious to be helpful, he never flaunted his learning and experience but managed to convey to his juniors the flattering and encouraging impression that any suggestions they made to him were at least as worthy of consideration as his own opinions. His ability to keep up to date with research progress in many different fields was astonishing—as was well illustrated by his making himself one of our leading authorities on the hazards of nuclear energy after the end of the war. He could and did continue to educate himself to the end of his long life. It was a rare pleasure to work for such a man, and I came to admire and respect him enormously during the years of our co-operation. It is sad indeed that we shall not again see his sprightly and perennially youthful figure, or encounter again his boyish enthusiasm, backed unobtrusively by deep knowledge and sound judgment, in promoting any cause which he believed to be important for the welfare of mankind.

Medical Notes in Parliament

MINISTER'S LAST APPEARANCE IN DEBATE ON HOSPITAL SERVICE

[FROM OUR PARLIAMENTARY CORRESPONDENT]

Mr. DEREK WALKER-SMITH, Q.C., on the eve of returning to his earlier love at the Bar, made his last bow on the Government front bench on July 21, when as Minister of Health he answered a debate on the hospital services. The news of his resignation was made known the next morning.

Defects of Leadership and Administration

The half-day debate, initiated by the Labour Party, was concerned with shortcomings in the N.H.S. hospitals, and the criticisms and suggestions made in it came from both sides of the House. Dr. EDITH SUMMERSKILL (Warrington, Lab.) brought the general charge of lack of co-ordination in policy and absence of first-class administration. The Health Service, she said, should be measured by the degree of integration of the three parts—hospitals, general medical and dental services, and the services administered by the local health authorities. Only when this co-ordination had been secured and the emphasis placed on preventive work and the domiciliary services would the hospitals be used intelligently and economically. The doctors at the B.M.A. conference at Torquay had been highly critical of the Minister's inadequate planning. This was surprising, as the B.M.A. was a Conservative organization. One would have thought that, with a Conservative Government in power, the doctors would have dealt tenderly with the Minister. Far from it.

No doubt greater attention would be paid to complaints about the maternity services and the failure to implement fully the Cranbrook Report since the startling report on maternal deaths between 1955 and 1957. The report had been leaked to the press. It should galvanize the Minister into action. What it revealed was reminiscent of conditions in the early part of the century, and it was an indication of the deterioration of the Health Service under Conservative administration. It was reported that more than 180 women died after caesarean operations, that sometimes these had been done by inexperienced people, and sometimes a consultant was called too late. In all these cases there should be a follow-up to find out precisely why there was inadequate attention. She complained also of a failure to provide adequate facilities for training dentists, of waste of public money on drugs—had the Minister really promised the vultures of the pharmaceutical industry yet another six months to make their unholy profits at the expense of the community?—and the bad conditions and pay of non-medical staffs.

Time Wasted on Trivialities

Lord BALNIEL (Hertford, Con.) was gratified to find in the Ministry's latest annual report news that the hospital building programme had now entered a period of steady expansion. Nevertheless, although expenditure on new building had increased from £10m. in 1955–6 to £31m. next year, in real terms less was being spent than in 1939. As a one-time member of the regional board concerned, he did not mince his words about pettifogging, trivial, bureaucratic interference by the Ministry in connexion with the new Welwyn Garden City and Hatfield Hospital. An entire year passed because of a dispute about whether the

boiler-house of this £2m. project should be a few feet larger or smaller, and ultimately there was a ministerial decision to which the regional board had to bow. He quoted the board's report for statements that the preliminary plans were discussed with the Ministry in 1954 and the authority to go to tender was received in July, 1958. Regional boards, he urged, should be given a wide measure of freedom. The Ministry having decided that a certain sum could be spent on a hospital, the regional board should be left completely free. There should be far greater autonomy all down the line—the Minister should be given far greater discretion by the Treasury, and hospital management committees should have far greater autonomy in the management of their own affairs.

Greater Integration with Hospitals Needed

Mr. L. PAVITT (Willesden, West, Lab.), after making the point that the status of the Minister of Health had been down-graded by his exclusion from the Cabinet, spoke up for greater integration of general practitioners and local health authorities with hospitals, using as an illustration the experience at Chadwell Heath Hospital, Essex, where pathological, *x*-ray, and sterile syringe services had been made available to general practitioners. Since this had been done the number of references to out-patient departments from about a dozen practices had been cut down by half. A similar scheme at Nelson Hospital, Merton, however, had come to an end because of insufficient staff. Not only were some buildings archaic, but the structure of hospital staffing was antiquated and the Government had failed to modernize it. When was something going to be done for the S.H.M.O.s and the time-expired registrars? The Minister might put a squib behind the Platt Committee, as had been done when the railwaymen were waiting for the Guillebaud report. It was time also that the problem was tackled of the huge chasm between the teaching hospitals and the hospitals under regional boards, who were taking the bulk of the work and had more than earned parity of status.

Sir OTHO PRIOR-PALMER (Worthing, Con.) added a local example of delay in hospital planning—discussions begun in February, 1956, but no finalized plan by last March—and quoting a sentence in a letter from the Minister that building takes time, commented, "Of course it does, but it takes a great deal longer if it is four years before one lays the first brick." Mrs. EVELINE HILL (Manchester, Wythenshawe, Con.) said that far too much time was wasted between management committees and regional board, and regional board and central administration. Experience led her to think it advisable that more power should be given to regional boards, "the people on the spot." Mr. JOHN MACKIE (Enfield, East, Lab.) endorsed the plea for less interference with building from Whitehall—"it is quite appalling"—and advocated the provision in hospitals of beds for mothers to stay the night when their children were admitted after accidents.

Too Tender to Medical Interests

Mr. KENNETH ROBINSON (St. Pancras North, Lab.) commended the Minister for having stood firm against Treasury pressure to cut the announced building programme. But he had found the Minister, in his role as a reconciler of interests, excessively tender to the medical interest—though this had not prevented him being criticized by the doctors at their conference. A Ministry which was having a perpetual running battle with the medical profession probably would not result in a particularly efficient hospital service. But where there was a conflict between the interests of the patients and the interests of the doctors it was the duty of the Minister to see that the interests of the patients prevailed. That was not by any means always done. He could have insisted on the Cranbrook Committee's proposal for an obstetric list being implemented, instead of which, because the B.M.A. objected for some misconceived notion of professional prestige, nothing had been done for 15 months, during which time dozens of women had died unnecessarily in childbirth. He repeated the complaints about consultants leaving far too many of their duties to registrars—specific cases seldom came to light, he said, because the Ministry had come to be regarded as being automatically on the side of the consultant, and people who knew of cases were afraid to report them—and of patients being persuaded to take private treatment to get priority for a hospital bed.

Progress to Better Conditions

Mr. WALKER-SMITH commented on the size of the Health Service—2,641 hospitals, over 7,000 consultants and 12,000 other doctors in them, 194,000 nurses, 12,000 midwives, and some 233,000 other employees, with a revenue account of more than £400m. a year. It was an enterprise labouring under inherited disadvantages. Generally speaking, hospital building reflected a pattern of disease and treatment which was not the pattern of to-day. To give the best service they had to extend and modernize hospitals and build new ones, and to make the best use of existing facilities.

The waiting-list figures (476,000) imposed two clear duties: to operate a fair system of admission, and to improve methods and expand accommodation. Last year there were four million courses of in-patient treatment, a 3% increase on 1958. Many improvements which achieved better working conditions, better treatment, and increased turnover did not mean an increased number of beds. Solid progress was being maintained in the better use of out-patient resources. In the last four years the number of attendances at out-patient clinics had been increased from 37,000,000 to 41,250,000, reflecting the shift of emphasis from institutional care to care within the community.

Report on Maternal Deaths

He explained that proofs of the report on maternal deaths were given in advance of publication to the *British Medical Journal* because there were many distinguished gynaecological and obstetric experts in London for the opening of the new building of the Royal College, and it was desired that some comment should be available for them. The *Journal* had said, rightly,* that there were cases where elementary precautions were not taken and serious mistakes made. That was most regrettable, but it was not true that all the avoidable factors were of that kind. One of the commonest avoidable factors was the failure by a patient or her family to take the advice given, or even to seek professional care at all. The scope of the report should also be kept in mind. It dealt with 861 maternal deaths due to childbirth in a period when there were 1,112 such deaths but more than two million births. It showed a decrease of more than one-fifth in maternal deaths since the first report was published in 1957, and that despite a rising birth-rate. Improvement depended on better antenatal care, better health education, better selection of cases for hospital care, and so on. The Report hammered all this home in an effective way which of itself was bound to lead to improvement.

Building Programme

The hospital building programme had now gathered pace and was going forward in a satisfactory way. By the beginning of this year there were 180 major schemes at various stages of building or planning: eight new hospitals were partly completed and partly brought into use; nine were started; 17 were at the planning stage. They were seeking to improve design and quality and to accelerate procedures to quicken construction. He had been very concerned about administrative procedures in respect of approval and so on, and it would not be long before more information could be given about the improvement of them.

The Estimates were carried by a vote of 218 votes to 149.

**British Medical Journal*, July 9, p. 123.

Nuffield Grant for Industrial Health Services

The MINISTER OF LABOUR announced on July 25 that the Nuffield Foundation Trustees had allocated £250,000 for the further development of group industrial health services and industrial hygiene services. He said the money would be applied to assist practical schemes which promised to be self-supporting after an initial period of development. He recalled that group schemes had been operated successfully in a few places with special circumstances such as Slough and Harlow, both new towns, and where the factories were grouped, and explained that it was hoped in this new work to extend it to older areas and areas where factories were scattered.

QUESTIONS IN THE COMMONS

General Practitioners' Compensation

Mr. JOHN EDEN (Bournemouth, West, Con.) asked on July 11 how much compensation, due under Section 36 of the National Health Service Act, 1946, had not yet been paid to doctors; and how much was being paid to them annually by way of interest at 2¾%. Mr. WALKER-SMITH stated that the amount outstanding on June 30, 1960, was £35,740,000, and gross interest paid during the year ended on March 31, 1960, was £1,040,000.

Antiquated Hospitals and Temporary Buildings

Mr. H. BOYDEN (Bishop Auckland, Lab.) wanted to know how many hospitals were either substantially over 50 years old or mainly composed of temporary buildings erected more than 15 years ago. Mr. WALKER-SMITH told him on July 18 that the information available showed only the dates at which hospitals were originally erected, but not the date or extent of subsequent alterations and improvements over the period in question: 1,400 hospitals now in use were originally erected before 1910, and 90 mainly consisting of temporary buildings had been in use for more than 15 years.

Patients Seen by Juniors

Mr. WILLIAM GRIFFITHS (Manchester, Exchange, Lab.) asked the Minister whether he would give an assurance that patients referred by general medical practitioners to hospital out-patients' departments for the purpose of obtaining an opinion of a doctor of consultant status were not seen only by a junior doctor engaged upon his pre-registration training. Mr. WALKER-SMITH said that it would not be appropriate for an out-patient to be seen only by an unsupervised, provisionally registered house-officer, and he had no evidence that this occurred. Some part of the investigation might properly be delegated to such junior staff under the consultant's responsibility. Mr. GRIFFITHS said that this sometimes happened in certain hospitals and offered to send the Minister details for investigation. Mr. WALKER-SMITH said he would look into them; but the principle was as he had stated.

Trial of Oral Polio Vaccine

Lord BALNIEL asked what arrangements had been made for trials in the use of oral live poliovirus vaccine; and how soon the Minister expected to decide whether such vaccine could be used in the immunization programme. Mr. WALKER-SMITH said that the Medical Research Council were carrying out small-scale trials of the Sabin oral vaccine. A decision as to the use of oral vaccine in this country's vaccination programme was unlikely to be reached for some time yet, as it would depend on the outcome of these trials and on the experience that was being gathered in other countries, and those who were eligible would be well advised to come forward now for vaccination under the current arrangements, if they had not already done so.

Doctors' Telephone Numbers

Mr. JAMES DEMPSEY (Coatbridge and Airdrie, Lab.) asked the Postmaster-General if he would post the names and telephone numbers of local doctors in a conspicuous part of telephone kiosks for the convenience of the general public. Mr. J. R. BEVINS stated on July 20 that he had recently arranged for lists of Health Service doctors to be available in telephone exchanges, so that inquiries from both kiosks and private telephones could be dealt with. These lists were also held at the larger post offices. He believed that these arrangements, and the 999 service, provided the best way of meeting this public need.

Medico-Legal

RADIONICS AND THE BLACK BOX

JUDGMENT FOR DEFENDANT

[FROM A LEGAL CORRESPONDENT]

As we reported briefly last week (July 23, p. 318) Mr. Justice Davies gave judgment for the defendant, on July 18, in this action by Miss Catherine Olivia Philips, of Four Winds, Porlock, Somerset, against Mr. George Walter de la Warr, of Raleigh Park Road, Oxford, for damages for fraud. Details of the trial were given in our issues for July 9 (p. 156) and July 16 (p. 214).

Issues for Decision

His Lordship said that the issues were these: was it true that the box was bogus and that it was incapable of diagnosis or treatment? Was it proved that the defendant did not honestly believe in it? Did the defendant have no honest belief in Miss Philips's ability to work the box? The underlying theory was that every one of us, and everything in the world, and every part of us, radiated rays and it was possible, by using this box, to pick up these radiations. Nobody had suggested that they knew how the box worked; the standard nailed to the mast by Mr. Humphreys were the famous words of Galileo spoken many years ago, with the slight alteration of one word: "but it works all the same."

It had been emphasized that all the diagnosis and treatment took place on the pre-physical plane, or perhaps more accurately the para-physical plane. But if the system was to work at all, then the end product must be on the physical plane, and the witnesses plainly thought so. It was only common sense that if a person was suffering from a chronic illness it did not matter on what plane he was being treated so long as he was cured. Mrs. de la Warr had said that they could not cure anything physical or treat anything physical; they just believed that they could administer mental treatment which they hoped would react beneficially on the physical state of the patient. In his Lordship's opinion that was putting the claim much lower than it really was.

It was all part of the de la Warr optimism that if a thing worked that was good; if it worked in the wrong way that was interesting. Possibly these people found difficulty in coming down to the ground where most of us had to live. A large number of exaggerated and extravagant statements had been made; but what his Lordship had somewhat unjudicially called "shooting a line" was not necessarily inconsistent with a genuine belief. People often made extravagant claims for things they believed in. There had also been a marked lack of clear and logical thinking on the part of Mr. de la Warr and his associates. It was true that the de la Warrs made a good living out of radionics; but that did not mean that Mr. de la Warr must be an impudent charlatan.

Body of Opinion "Impossible to Ignore"

It was quite plain that there existed a great body of opinion favouring a belief in radionics, and a number of reputable witnesses had given evidence to the effect that

they believed in the work of the de la Warrs and in his theories and in his system. It was utterly impossible to ignore that body of opinion. The remarkable thing was that Miss Philips had not been able to call one single witness to say that he had purchased a box and thereafter failed to use it, or someone to say that he was treated radionically to no effect. His Lordship would add to that the fact that there had been in existence, since 1939, a Medical Society for the Study of Radionics, to which some twenty members of the medical profession belonged.

In spite of all the criticisms to which Mr. de la Warr himself was open, his Lordship was impressed with the manner in which Mr. de la Warr, his wife, and daughter had given their evidence; on all the essential matters in this case—namely, their belief in the efficacy of the box as a diagnostic instrument, and incidentally in the camera, and in the latent ability of Miss Philips to operate the box—his Lordship had no doubt, and so found, that they were telling the truth. Mr. de la Warr, and of course his daughter, who gave both lessons, honestly believed that Miss Philips had the ability to operate the box. That finding was decisive in this case, but it was right that his Lordship should emphasize that he was certainly not deciding that it had been proved that the box did in fact work for either diagnosis or treatment. On the evidence that was a very open question. Still less was he making any finding that the camera was genuine. It was not necessary to come to any conclusion about the camera, but in his Lordship's opinion the totality of the evidence strongly suggested that the camera was completely bogus, and the images fakes. However, his Lordship was satisfied that the defendant believed in the camera no less than he did in the box. Accordingly, the action failed, and there would be judgment for the defendant.

SUICIDE AND LIFE INSURANCE

[FROM OUR LEGAL CORRESPONDENT]

At an inquest on April 26, at Barnard Castle, a verdict of suicide was found on a Lance-Corporal of the 15/19 King's Royal Hussars (*Yorkshire Post*, April 27). It appeared that the Lance-Corporal, who had been in financial difficulties, had taken out an endowment insurance policy on his life, and four days later had thrown himself down 132 feet from a railway viaduct over the River Tees. Death was due to shock and haemorrhage due to injuries to his back and pelvis.

A Cigarette Between his Lips

This case recalls the leading case[1] which arose out of the suicide of a certain Major Rowlandson in 1934. Major Rowlandson was insured for £50,000, but was unable to continue paying the premiums, and was granted until 3 p.m. on August 3, 1934, to pay. While riding down Pall Mall in a taxi on August 3 Major Rowlandson asked the driver to notice the time: when they turned into Albemarle Street he shot himself with a Service revolver, a half-smoked cigarette between his lips (*The Times*, June 30, 1936). It was a term of the policies that the insurance company was to pay in the event of the assured's suicide, sane or insane (a term not unknown in policies to-day). The House of Lords held, however, that the administratrix of the estate could not recover the policy moneys, since it is contrary to public policy that the courts should assist a man who has committed a felony (or his representative) to recover the fruits of his crime. That remains the law to-day. The representatives of a suicide have a good claim in law for the policy moneys only if at the time of the suicidal act the assured was legally insane and so not responsible for the felony of suicide. The jury in the civil action brought on Major Rowlandson's policies found that he was sane at the time that he killed himself. There is nothing, however, to prevent an insurance company making an *ex gratia* payment in cases of suicide.

Coroner's Verdicts

This state of the law raises the question of the form of the verdict at the coroner's inquest on a suicide. The Coroner's Rules prescribe a finding in the form: "C.D. killed himself [whilst the balance of his mind was disturbed]." The words in square brackets are optional. A coroner's verdict using the words in the brackets cannot be relied on in a civil action on an insurance policy. The words do not indicate legal insanity, and, even if they did, a civil court would not be bound by the finding, but would require proof of insanity by proper evidence.

A coroner's inquest is not directed to the state of mind of the accused, and the phrase "balance of the mind disturbed" or "of unsound mind" is an anachronism retained on sentimental grounds. Until 1870 the goods of a person who had committed *felo de se* (self-murder) were forfeited to the Crown, and until 1832 his body was buried at the cross-roads with a stake driven through it, without religious ceremony. The alternative verdict of suicide while of unsound mind avoided these consequences of *felo de se*, and when the penalties had been abolished the phrase "of unsound mind" was still usually used to avoid the stigma of the harsher verdict. The disappearance of the verdict of *felo de se* following the recommendations of the Departmental Committee on Coroners of 1935[2] has removed the real usefulness of the phrase. However, a finding that the balance of the deceased's mind was disturbed is often made on little or no evidence. The Divisional Court of the Queen's Bench Division has recently urged[3] that such a finding ought to be made only if based on evidence given at the inquest. The Court also doubted whether the verdict is as kind as it is often thought to be. The Departmental Committee said that the verdict with its suggestion of insanity in the family sometimes had adverse reactions on other members of the deceased's family.

[1] Beresford *v.* Royal Insurance Company Limited [1938] AC 586.
[2] Cmnd. 5070, 1936.
[3] R. *v.* Horner, *The Times*, May 16, 1956.

NEW TRIAL FOR HYPNOTIST

[FROM OUR LEGAL CORRESPONDENT]

On a new trial, on July 7, in the Coventry County Court, judgment was given in favour of Mrs. Jean Emma Dyke in her action for the return of £53 paid as fees to Victor Vinmar (George Joseph Cassidy), of Upper Fitzwilliam Street, Dublin (see *Journal*, March 12, p. 813; April 9, p. 1143).

The court did not find all the allegations against Vinmar proved, but it was satisfied that Mrs. Dyke had shown that Vinmar had failed to conduct himself in a proper and seemly manner during her treatment.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part II*: [1 2 3]M. I. J. Andrews, [2]T. C. M. Andrews, [1 2 3]D. R. Bailey, [2 3]D. R. Bainbridge, [2]A. J. C. Balfour, [3]J. K. Bamford, [1 2 3]J. H. J. Bancroft, [1 2 3]T. M. Barratt, [1 2]M. H. Bartlett, [3]P. F. Bates, [1 2 3]J. S. R. Baxter, [1 2]R. J. E. Bellars, [1 2]B. Blackwell, [1 2]R. W. Blamey, [2]J. S. Bland, [1 2]W. K. Blenkinsopp, [1 2]W. J. Boerema, [1 2 3]R. P. Boggon, [2]B. S. Bowers, [1 2 3]D. J. Bradley, [1 2 3]D. P. Brenton, [1 2]I. F. Brockington, [1 2 3]A. F. A. Brown, [1 2]N. M. S. Brown, [1]M. T. T. Bryant, [1 2 3]E. Byrne-Quinn, [1 2 3]H. C. Cameron, [1 2 3]A. Catterall, [1]C. C. Chan, [2 3]H. Cheng, [1 2 3]G. P. Clein, [1 2 3]E. Clow, [1 2 3]R. J. Cockerill, [1 2 3]R. A. F. Cox, [1 2 3]K. W. E. Craven, [1 2 3]P. H. Curry, [1 2 3]A. O. Davies, [2]R. N. Davies, [1 2 3]R. S. Dean, [2 3]M. J. Denham, [1]C. J. Dingle, [1 2 3]J. W. H. Doar, [3]R. S. W. Dowling, [1 2 3]C. D. M. Drew, [1 2 3]P. W. Dutton, [2 3]J. R. Eames, [3]W. D. Edwards, [1]R. H. Eleady-Cole, [1 2 3]A. R. Elkington, [1 2 3]P. B. C. Fenwick, [1 2]J. R. H. Fisher, [1 2 3]J. A. W. Fitzgerald, [1 2 3]S. M. FitzGibbon, [1 2 3]J. Fletcher, [1 2]A. E. Forbes, [1 2 3]K. J. Fox, [1 2 3]R. M. Frew, [1 2 3]D. L. Froggatt, [1]G. W. Gamler, [1 2]J. R. Garnham, [1 2 3]J. D. Geddes, [1]A. E. Gent, [1 2 3]H. K. A. Ghazaleh, [2]D. F. Gibson, [1 2 3]S. M. Gibson, [1 2]A. J. Gordon, [1]W. D. Graham-Brown, [1 2 3]D. J. P. Gray, [1 2 3]C. J. Griffiths, [1 2 3]N. J. Gross, [1 2]I. W. F. Hanham, [1 2 3]E. Hardy, [1]W. D. Harper, [1 2 3]P. W. R. Harris, [1 2 3]W. G. Hartfall, [1 2]A. R. H. Hastie, [2 3]L. J. H. E. Hayek, [1 2 3]R. J. Heald, [1 2 3]K. W. Heaton, [1 2 3]C. Heulghan, [1 2 3]T. G. Hewlett, [1 2 3]M. C. Holderness, [1 2 3]J. H. Holland, [1 2]G. D. Ingram, [1 2 3]G. J. Johnson, [1]A. J. Johnston, [1 2 3]J. S. Kirkham, [2]R. A. Knight, [1 2 3]D. Knight-Jones, [1 2 3]G. Laszlo, [1 2 3]N. J. P. Lehmann, [2]M. J. Leverton, [1 2 3]F. C. Leyland, [1 2 3]C.-C. Lim, [1 2 3]K. A. Macdonald-Smith, [1 2 3]A. A. McFarlane, [2]R. K. Mackenzie Ross, [1 2 3]D. B. Mackie, [2 3]I. C. McLellan, [1 2 3]B. E. H. Maden, [1 2]C. N. Mallinson, [1 2 3]E. S. Marsden, [1 2 3]F. P. Marsh, [1 2 3]L. P.

Martin, [2 3]B. R. Middleton, [1 2 3]P. A. H. Millac, [1 2 3]C. H. Mills, [1 2 3]A. M. D. Mitchell, [1 2 3]M. J. Mitchinson, [1 3]R. S. Moore, [1 2 3]T. F. Mortimer, [1 2 3]J. M. Newsom Davis, [1 2 3]P. J. F. Nicholson-Lailey, [1 2 3]A. D. C. Norris, [1 2 3]R. C. L'E. Orme, [1 2 3]J. R. Parker, [1 2 3]W. L. Parry-Jones, [1 2 3]H. R. Patterson, [1 2 3]J. H. Pennington, [1]J. Pilcher, [1 2 3]E. Platts, [1 2 3]L. F. Prescott, [1 2 3]I. M. Rabinowicz, [1 2 3]R. A. Randell, [1 2 3]D. R. Redwood, [1 2 3]I. D. B. Rennie, [1 3]M. H. C. Rice, [1 2 3]P. Richards, [1 2 3]G. M. Riches, [1 2 3]W. D. Riding, [1 2 3]S. O. B. Roberts, [1 2]Mrs. J. M. Robson, [1 2 3]B. Rowe, [1 2 3]S. J. E. Russell-Wells, [1 2 3]J. D. Scobie, [1 2 3]M. T. Scott-Kerr, [1 2 3]A. T. Seaton, [2]R. B. Sellwood, [1 2 3]B. A. Senewiratne, [1 2 3]J. H. Sheldon, [1 2 3]D. E. Sibson, [3]B. Simpson, [1 2 3]I. McD. Simpson, [1 2 3]A. F. Smith, [1 2 3]M. E. Snell, [1 3]T. H. Spreadbury, [1 3]Hon. T. C. B. Stamp, [1 2 3]P. R. C. Steele, [1 2 3]G. M. Sterling, [2 3]T. J. H. Sweeting, [1 2 3]B. J. Sykes, [1 3]F. J. B. Taylor, [1 2 3]J. H. Taylor, [1 2 3]D. F. E. Thallon, [1 3]J. H. Thornley, [1 2 3]R. H. C. Vaux, [1 2 3]G. D. Walker, [1 2]P. E. Walker, [1 2 3]R. Warrington, [1 2 3]J. P. Watson, [1 3]F. W. Webb, [1 2 3]M. M. Webb-Peploe, [1]R. C. Westbury, [1 2 3]R. W. B. White, [1 3]A. J. Whitworth, [1 2 3]J. L. Wilkins, [1 3]E. D. G. Williams, [1 2 3]E. R. Williams, [1 2 3]T. J. Willis, [1]J. D. S. Wilson, [1 2 3]P. H. L. Worth, [1 2 3]P. L. Wright, [1]L. I. Zander. *Part I (Pathology and Pharmacology)*: T. C. M. Andrews, M. H. Bartlett, R. P. Boggon, B. S. Bowers, N. M. S. Brown, M. T. T. Bryant, T. F. C. Dibble, C. J. Dingle, M. C. Doddridge, P. A. Draper, J. H. J. Durston, A. R. Elkington, P. B. C. Fenwick, J. A. W. Fitzgerald, S. M. FitzGibbon, A. E. Forbes, R. M. Frew, S. L. Geohegan, D. F. Gibson, A. V. Gillespie, W. D. Graham-Brown, P. S. E. G. Harland, L. J. H. E. Hayek, M. Hayward, T. G. Hewlett, W. F. G. Hulley, R. F. Jowers, N. J. P. Lehmann, R. D. B. Leicester, A. A. McFarlane, A. W. McKenzie, I. C. McLellan, B. E. H. Maden, R. S. Moore, P. J. F. Nicholson-Lailey, S. E. Odamtten, R. C. L'E. Orme, D. Pye, J. P. Recordon, J. H. Sheldon, G. M. Sterling, T. J. H. Sweeting, P. E. Walker, T. J. Willis, J. D. S. Wilson, L. I. Zander.

[1]Passed in principles and practice of physic. [2]Passed in principles and practice of surgery. [3]Passed in midwifery and gynaecology.

In Congregation on June 24 the degree of Sc.D. was conferred on M. de Burgh Daly, M.B., B.Chir.

UNIVERSITY OF ST. ANDREWS

At a Graduation ceremonial on June 28 the following degrees were conferred:

M.D.—H. T. Howat (with honours and a University gold medal), J. R. Rintoul (with high commendation).

CH.M.—J. Grieve.

M.B., CH.B.—[1]M. J. Weiner, [2]S. Wain, [2]W. R. Porter, [2]M. G. Barker, J. F. Agnew, Barbara Ainsworth, P. J. Ashworth, I. C. Baxter, M. M. Besen, Elizabeth A. Blair, W. Boodish, T. C. K. Brown, E. A. O. Bucknor, R. Coulthard, D. J. Cowley, K. Davidson, D. McG. Duncan, E. M. Duncan, Alison M. A. Elder, G. C. Ferguson, J. B. Ford, J. C. Forrester, W. McG. Gardiner, F. J. Gibbins, O. P. Goertz, J. M. Haddadin, C. S. Hampton, P. J. Hirsch, A. L. Honeyman, Elizabeth M. Husband, C. M. Iskander, A. Kaufman, R. E. Lea, P. W. Leech, J. Leslie, Margaret S. R. McEwan, F. McGrory, L. MacD. Mackenzie, R. A. S. MacLean, I. G. Mannall, T. G. Napier, T. D. Osafo, D. MacL. Piercy, J. Politi, D. R. Roberts, Elizabeth S. Ross, D. Sapsford, Vida A. Skinner, M. McD. Smith, A. G. Stewart, Elizabeth M. Sutherland, Anne Wannop, Joyce M. Watson.

[1]With honours. [2]With commendation.

UNIVERSITY OF GLASGOW

The following degrees were conferred on July 9:

M.D.—[1]J. F. Boyd, [1]M. B. L. Craigmyle, [1]Eileen E. Hill, [1]I. M. Macgregor, [1]L. S. Scott, J. M. Smith.

CH.M.—[1]J. R. Kenyon, [1]F. C. Walker.

PH.D.—I. A. Carr, M.B., Ch.B., W. A. Crawford, M.B., Ch.B.

M.B., CH.B.—N. Ahmad, Marilyn G. Alberga, T. Alcorn, E. Anderson, J. F. Anderson, I. J. M. Barretto, G. Bell, J. W. Black, M. A. Bodin, I. E. Boyd, [1]J. A. Boyle, N. T. Bratten, C. M. Brown, Sheila H. Brown, E. C. Buonaccorsi, D. MacL. Campbell, R. N. Cannon, I. A. Carter, R. K. Chatfield, [1]Elizabeth E. Chatton, Mary L. Cochran, A. N. Conner, M. D. Cosgrove, Isabella G. Crerar, R. B. Cunningham, Mary J. Delaney, J. P. Donachie, F. H. Donald, J. P. Donald, A. J. M. Donnachie, Anna K. Donner, R. N. C. Douglas, Margaret J. P. Duncan, M. S. Duncan, A. McK. Dyer, J. A. N. Emslie, R. R. Ewart, J. H. Ferguson, H. J. Fields, Winifred E. I. Finlay, [1]Janet P. Finlayson, K. H. Fisher, R. S. Fleming, R. J. F. Foulis, Eileen A. Gallagher, Mary Gallagher, W. J. A. Gibson, I. N. Gilchrist, J. T. Y. Gillies, Sheina E. W. Gillies, A. C. A. Glen, E. S. Glen, [1]A. M. Gordon, R. M. Graham, A. R. G. Handscomb, R. McG. Harden, M. G. Harris, R. T. Harrison, I. R. Hart, Ann E. Harvey, Anne L. Herd, W. C. Hetherington, N. S. Hodanu, I. M. D. Jackson, A. L. Johnson, [2]D. Johnston, M. Johnstone, D. Kelly, Sheila M. King, M. G. C. Kinghorn, Moira R. McL. Lang, A. G. Levin, J. Lind, [1]G. D. Lister, A. R. Lorimer, J. R. Lorimer, Anne E. P. Loudon, D. L. MacBeath, Maureen McCann, N. W. McCarry, J. McCarthy, Fiona R. Macdonald, Elizabeth F. McDonnell, S. M. McDougall, Jean T. Macfarlane, I. MacInnes, A. M. Mackay, Agnes F. H. McKerracher, R. F. MacLachlan, K. T. P. McMillan, W. McMurray, H. B. McNamee, A. J. Mack, M. Mahoney, Katherine E. Mann, A. J. Martin, H. C. Mason, A. W. F. Miller, J. Milligan, Alison E. Mitchell, E. A. Muir, Adele T. Mulholland, J. T. Murphy, A. S. Murray, J. A. Murray, R. B. Napier, I. Nicolson, J. O'Neill, E. A. Osborne, Elizabeth G. Pate, A. G. Patrick, M. Peacock, Phyllis Puckel, M. J. Pullen, Carolyn E. Ritchie, J. G. Rogerson, J. R. Rothnie, R. I. Russell, J. L. Sagar, I. F. M. Saint-Yves, R. D. F. Scorgie, A. O. Senbanjo, G. M. Smith, A. A. Spence, Isobel A. Stevenson, T. Stewart, Rachel A. M. Tait, Lillious McL. Taylor, W. D. Taylor, I. E. Thompson, J. Thomson, J. P. Vance, B. W. McW. Walker, A. S. Wallace, R. J. Weir, J. D. Welch, Jean R. K. White, Helen McL. Wishart, R. H. Wood, Elizabeth J. W. Wright, J. A. Young, J. R. B. Young, G. H. Zarghami.

[1]With commendation. [2]With honours.

UNIVERSITY OF ABERDEEN

At a Graduation ceremony on July 7 the following degrees were conferred:

M.D.—[1]M. MacLeod, [1]H. G. Smylie, [2]A. Gatherer, [2]G. A. McDonald, [3]Marguerite McD. Pereira (née Scott), [3]W. J. S. Still (*In absentia*), [2]A. J. Watson, C. G. Clark, P. E. G. Mitchell.

CH.M.—R. A. Stephen.

PH.D.—Manik Singh, M.B., B.S.

M.B., CH.B.—[1]Anne M. Wyllie, [2]S. D. Preston, [2]A. I. G Davidson, [2]Joan Lees, [2]G. A. Batson, C. C. Adomakoh, Anne B. M. Anderson, J. F. R. Bowie, Joan A. Bremner, Jane I. Bruce, R. Buchan, Ann P. Carter (née Bradford), J. K. Cheriyan, W. G. B. Clark, T. P. Crosgrove, Erica D. Cundill, Margaret Cunningham, J. G. Donald, R. W. M. Downie, R. W. Duncan, D. Durno, Johanna E. U. M. Ehrhardt, Evaline A. J. Gammack, A. J. S. Gardiner, T. A. Goodbrand, R. L. Gordon, G. D. Gormley, J. R. Greig, A. S. Hunter, N. R. Johnston, Margaret A. Jones, Shirley Jones, Allison M. Kennedy (née Sleigh), B. R. Kennedy, F. H. G. Lakin, R. M. Logan, M. D. Lowe, Margaret T. McCallion, A. G. Macdonald, C. Mackay, A. A. W. McKechnie, R. N. Mackie, R. D. M. MacLeod, K. J. MacRitchie, R. Miller, A. Morgan, L. D. Morrison, W. McG. Park, A. F. Pringle, J. B. L. M. Robb, P. W. Ross, K. A. Smith, J. A. Thom, O. A. Thores, W. R. C. Turner, J. A. Wattie, A. R. White, G. G. Whyte, J. F. Wood.

[1]With honours. [2]With commendation.

At Graduation ceremony on July 8 the honorary degree of LL.D. was conferred on Lady May Deans Baird, M.B., Ch.B., Chairman of the North-eastern Regional Hospital Board, Scotland, and Sir David Campbell, Regius Professor of Materia Medica in the University from 1930 to 1958, and President of the General Medical Council.

The following prizes and medals were awarded for the session, 1959–60: *Anderson Gold Medal and Prize in Clinical Medicine*, A. J. S. Gardiner. *Alexander Smith Cardno Prize in Anatomy* and *Silberg Prizes in Anatomy and Physiology*, M. L. Diament. *Chanock Gold Medal in Anatomy, Durno Prize in Anatomy, Fife Jamieson Gold Medal in Anatomy*, and *Lizars Gold Medal in Anatomy*, N. B. Bennett. *Dyce Davidson Memorial Gold Medal in Materia Medica*, R. S. Chapman. *Matthews Duncan Gold Medal in Obstetrics*, Erica D. Cundill. *Keith Gold Medal in Surgery*, A. I. G. Davidson. *MacQuibban Prize in Medicine*, R. N. Mackie. *MacQuibban Prize in Surgery, Murray Medal and Scholarship*, and *Davidson Smith Prize in Diseases of Children*, Anne M. Wyllie. *Ogston Prize in Surgery*, Jean I. Morrison. *Shepherd Memorial Gold Medal in Surgery*, R. L. Gordon. *John A. Watt Prize in Preventive Medicine*, J. A. Oshikanlu.

Dr. C. J. H. Mann has been appointed Lecturer in Public Health and Social Medicine from October 1, 1960.

UNIVERSITY OF DURHAM

In Congregation on July 1 the honorary degree of D.Sc. was conferred on Dr. Donald Hunter, physician to the London Hospital and director of the Medical Research Council department for research in industrial medicine.

The following degrees and diplomas were conferred on July 1 and 2:

M.D.—S. Brandon, F. L. Constable, W. R. Dodds, [1]H. Madgwick.

PH.D.—*In Medicine*: [1]Maung Pe Thein.

M.B., B.S.—A. Badohu, N. R. Batey, Rose M. Bell, M. J. Blaiklock, B. C. Bradley, R. A. L. Brewis, Mary Burdus, G. M. Burke, Jennifer D. Burkett, Merica D. M. Carey, Sylvia Carr, Valerie Clarke, Ruth Cohen, Gillian K. Craven, D. R. Cullen, [1]J. B. Cunningham, Joan Currah, G. Dale, W. N. Eastham, G. H. Eeles, M. S. Elbualy, Valerie H. Feltoe, J. B. Garston, I. D. Gilchrist, R. D. Hall, G. H. de G. Hanson, C. Harnarayan, [1]Elizabeth T. Hedley Whyte, Margaret Irvine, E. R. Irving, J. A. Jordan, A. B. Kargbo, [1]L. M. Kremer, I. Laurimaa, Marthe A. Le Dune, Elizabeth A. Letsky, F. Lustman, Angela C. McArdle, M. J. McCallum, P. P. Meisner, J. W. Muncaster, C. Nelson, R. Newman, P. A. Nicholson, M. Pawath, J. H. S. Pimblett, E. G. Robertson, A. I. Simpson, A. O. Sobo, Sheila Sproat, L. Strunin, Iris Swanson, P. J. Tallentire, Joan Taunch, J. P. Todd, Patricia A. M. Toohill, R. E. Walker, D. A. Walton, J. K. Ward, B. E. Welsh, A. Westgarth, G. E. Whittingham, Audrey Williams.

DIPLOMA IN PUBLIC HEALTH.—A. R. Buchan, J. Connolly, Margaret McN. Copland, Mary J. Danskin, J. Deegan, G. V. Griffin, Margaret A. Loraine, J. F. Mather, D. I. Robertson, M. Sackwood, J. Sarginson, Mary M. Szekely, Mary D. Taylor.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—Pamela Beamish, Valerie Matthews.

[1]*In absentia*.

ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the College on June 23: B. M. Andrea, W. L. H. Armstrong, J. MacA. Bremner, R. Britten-Jones, D. E. Cam, R. Campbell, D. B. Chrisp, J. J. Collins, W. J. Cook, J. M. Copeland, R. H. Dawson, O. W. Deacon, A. F. Ferguson, W. G. Ferguson, M. J. Flood, G. D. Forster, W. D. Friend, J. C. Gillman, F. J. Gruar, J. P. Halliday, J. M. Hay, D. G. Kermode, S. G. Koorey, H. M. Learoyd, Hin Seng Leong, G. C. Liggins, J. Ludbrook, S. A. Mellick, A. W. Middleton, J. P. Richardson, L. Rozner, C. H. Schneider, H. D. D. Tyer, M. Wald, E. C. Watson, G. Wynne-Jones.

FACULTY OF ANAESTHETISTS

The following, having satisfied the Court of Examiners, were admitted to Fellowship of the Faculty of Anaesthetists of the College on June 23: J. Loughman, D. C. Maxwell.

Vital Statistics

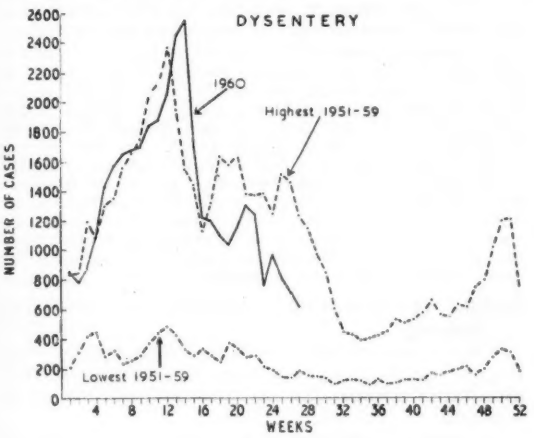
Road Casualties

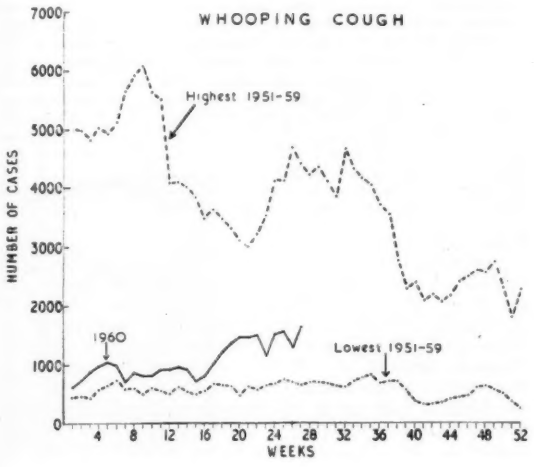
There were 504 deaths on the roads of Great Britain in May this year—12 more than in May, 1959. The seriously injured numbered 6,959, a decrease of 141 ; and the slightly injured 21,747, a decrease of 168. The figures are not strictly comparable because last year there were five week-ends in the month, including the Whitsun holiday. Motor scooter traffic, as estimated by the Ministry of Transport, was 17% higher in May this year than last year, but fatal casualties nearly doubled—22 this year compared with 12 last year.

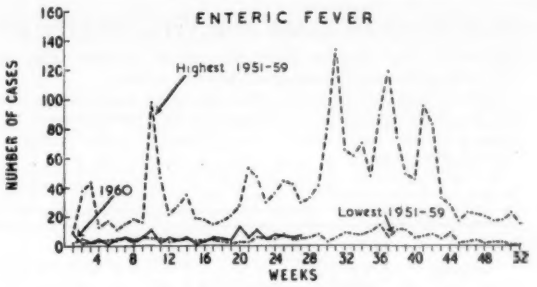
In the first five months of the year road deaths numbered 2,462, an increase of 346 on the corresponding period of 1959. Total casualties amounted to 124,412, an increase of 7,917 (6¼%); the increase in motor traffic was estimated at 10%.

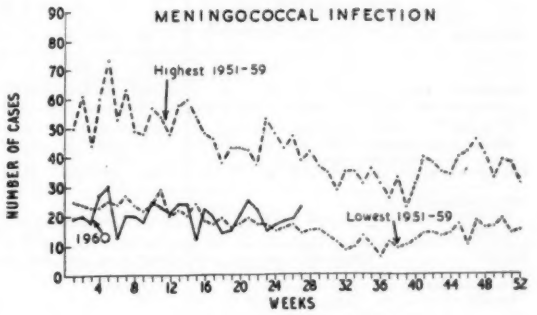
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending July 9	Week Ending July 16
Dysentery		
Durham	10	**21**
Essex	32	**40**
Romford M.B.	6	**14**
Kent	25	**53**
Cranbrook R.D.	0	**38**
Lancashire	129	**130**
Liverpool C.B.	21	**24**
Manchester C.B.	21	**14**
Accrington M.B.	9	**10**
Worsley U.D.	7	**15**
London	63	**63**
Islington	12	**15**
Lewisham	8	**19**
Norfolk	13	**19**
Norwich C.B.	9	**11**
Yorkshire North Riding	18	**12**
Middlesbrough C.B.	10	**10**
Yorkshire West Riding	75	**66**
Leeds C.B.	21	**13**
Glasgow	76	**59**
Measles		
Nottinghamshire	164	**291**
Nottingham C.B.	91	**196**
Acute Poliomyelitis		
London	3	**5**
Paddington	0	**2**
Devonshire	2	**4**
Plymouth C.B.	2	**4**
Food-poisoning		
Northumberland	5	**20**
Newcastle upon Tyne C.B.	5	**20**
Glamorganshire	16	**24**
Cardiff C.B.	11	**17**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 9** (No. 27) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	0	4	1		11	6	3	0	3
Dysentery ..	615	63	119	10	3	680	44	247	8	1
Encephalitis, acute	6	0	0	0		3	0	0	0	
Enteric fever:										
Typhoid ..	0	0	0	0		3	0	0	1	
Paratyphoid ..	7	3	0	0		5	0	0	0	
Food-poisoning ..	218	21	24	2		293	64	20	2	
Infective enteritis or diarrhoea under 2 years				13	19				14	24
Measles*	2,490	101	43	0	18	8,812	310	194	174	145
Meningococcal infection	23	2	19	0	1	15	2	8	2	1
Ophthalmia neonatorum	20	1	1	0		23	2	10	0	
Pneumonia† ..	147	8	98	4		158	9	112	2	
Poliomyelitis, acute:										
Paralytic ..	7	2	0	} 0	4	{ 31	5	1	} 2	
Non-paralytic ..	9	1	1			16	4	1		
Puerperal fever§ ..	148	14	10	1	1	199	20	10	0	
Scarlet fever ..	406	21	37	13	16	784	54	73	15	22
Tuberculosis:										
Respiratory ..	440	50	81	19		447	42	62	8	
Non-respiratory	63	6	18	7		62	9	13	0	
Whooping-cough	1,619	114	111	9	103	631	26	65	21	87

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0		0	0	0	0	0	0
Dysentery ..	1	0				1	0		0	
Encephalitis, acute		0			1		0			0
Enteric fever ..	0	0	0			0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	0		0	5	0	0	0	0
Influenza	5	0	0		0	3	0	0	0	1
Measles		0	0		0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	345	24	14		8	355	34	15	8	4
Poliomyelitis, acute	0	0			0	2	0		0	0
Scarlet fever ..		0	0		0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 49	{ 3	7		3	} 55	{ 5	4	1	3
Non-respiratory		0	0		0		0	2	0	1
Whooping-cough	0	0	0		0	0	0	1	0	0
Deaths 0–1 year ..	298	24	30		5	286	25	29	9	12
Deaths (excluding stillbirths) ..	8,564	705	540		132	8,402	670	499	110	122
LIVE BIRTHS ..	15,522	1255	1045		377	14,416	1227	1025	271	415
STILLBIRTHS ..	300	22	24			311	29	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

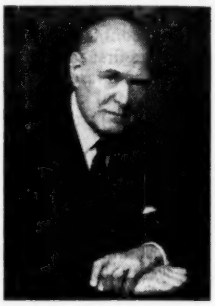
Medical News

Resignation of Minister of Health

Mr. D. WALKER-SMITH, who has been Minister of Health since 1957, has resigned to return to his practice at the Bar. He will continue in office for the present Parliamentary session. His successor has not yet been appointed. (*The Times*, July 23.)

New Chairman of Wellcome Trust

The appointment of Lord PIERCY to succeed Sir HENRY DALE, O.M., F.R.S., as chairman of the Wellcome Trust was announced in the *Journal* last week, p. 322.



Lord Piercy, who holds the B.Sc. Econ. of London University, is president of the National Institute of Industrial Psychology, and was president of the Royal Statistical Society for the annual term of office 1954 to 1955. From 1953 to 1956 he was chairman of the Committee of Inquiry on the Rehabilitation of Disabled Persons. He has other interests in the fields of commerce and education.

Sophia Jex-Blake Chair of Physiology, Royal Free Hospital School of Medicine

Dr. C. B. B. DOWNMAN, reader in physiology at the Royal Free Hospital School of Medicine, has been appointed to the Sophia Jex-Blake chair of physiology tenable there.

Dr. Downman qualified B.Sc. in 1937, and took his M.R.C.S. and L.R.C.P. from St. Thomas's Hospital Medical School in 1941. He took a Ph.D.Lond. in 1953. During 1938 he was junior demonstrator at St. Thomas's Hospital Medical School, and in 1939 spent some time as student medical officer at the South-west London Blood Supply Depot. In 1941 he was appointed to the teaching staff of St. Thomas's Hospital Medical School and proceeded to senior lecturer. In 1943 Dr. Downman was seconded for nine months to the National Institute for Medical Research, and in 1948 he exchanged posts with the senior lecturer in the department of physiology in the University of Otago. He joined the department of physiology at the Royal Free Hospital School of Medicine in 1954.

Institute of Orthopaedics: Museum of Orthopaedic Radiology

With the collaboration of the Royal National Orthopaedic Hospital, the Institute of Orthopaedics has provided new and larger premises for its Museum of Orthopaedic Radiology.

The collection, which contains over 10,000 fully classified and documented films, is divided into a general section and one covering all known disorders of bones and joints. It has been assembled by Dr. F. CAMPBELL GOLDING over a period of 25 years, and is being constantly revised and enlarged by its originator, his colleagues, and others. The new room, which leads off the radiology department, has seating accommodation with viewing space for 10 people. Reference may be made also to a classified and annotated collection of clinical photographs and prints of radiographs, collected since the earliest days of the Institute and developed chiefly through the efforts of Dr. R. O. MURRAY. The museum is open to all medical graduates and undergraduates, and workers in relevant fields.

Osler Club

The Annual Dinner of the Osler Club of London was held on July 11, with the president, Mr. A. DICKSON WRIGHT, in the chair. The Oslerian Oration was delivered by Professor Sir GEORGE PICKERING, F.R.S. A founder member of the Osler Club, he delivered its first communication, and his Oslerian Oration was in the form of intimate autobiographical reminiscences ranging from the inception of the Club in 1928 up to his appointment as a successor of Osler's at the University of Oxford and at 13, Norham Gardens. Mr. DICKSON WRIGHT proposed the health of

the guests, who included Dr. and Mrs. ALFRED WILHELMI, both professors of biochemistry at Emory University, Atlanta, Georgia. His Excellency Dr. F. T. CHENG replied. In the course of the evening Dr. BRYN THOMAS presented the Osler Club Medal to Mr. Dickson Wright, which has been created as a chain of office for the present and succeeding Presidents.

Biological Engineering Society

The Biological Engineering Society was inaugurated at a meeting held at the Royal College of Surgeons on June 10. The purpose of the society is to bring together doctors, physiologists, electronic engineers, mechanical engineers, and physicists from many parts of the country to further the applications of engineering to biological and medical problems. Professor R. WOOLMER, professor of anaesthesia, Royal College of Surgeons, was elected first president. The acting secretary, Dr. A. NIGHTINGALE, Physics Laboratory, St. Thomas's Hospital, London, S.E.1, will be glad to receive inquiries about the new society.

Transatlantic Yacht Race

Competitors in the single-handed yacht race across the Atlantic were asked by members of the Medical Research Council's division of human physiology at the National Institute for Medical Research to keep a log detailing such points as how much food and water they took, their sleep pattern, and their mood changes.

Dr. H. E. LEWIS, who works in the division and who has published work on human physiology during polar expeditions, says that the race provides a situation the conditions of which would be extremely difficult to reproduce in the laboratory. The competitors who record these details will be examined when they arrive in the States by members of the medical faculty of Columbia University. One doctor is taking part in the race—Dr. D. H. LEWIS, a general practitioner, who is sailing the five-ton sloop *Cardinal Vertue*.

Central Health Services Council

The Minister of Health, Mr. D. WALKER-SMITH, has made the following new medical appointments to the Central Health Services Council and Standing Advisory Committees:

Mr. T. HOLMES SELLORS,* Dr. S. THOMAS,* Dr. J. DENIS HILL* (*also appointed to Standing Medical Advisory Committee.) *Standing Advisory Committees: (Medical),* Dr. A. B. DAVIES, Professor T. MCKEOWN; *Mental Health,* Dr. MARY CAPES; *Cancer and Radiotherapy,* Dr. E. F. SCOWEN, Professor ANDREW SEMPLE, Professor F. A. R. STAMMERS.

Committee on Health Education

A Joint Committee of the Central and Scottish Health Services Councils has been appointed under the chairmanship of LORD COHEN OF BIRKENHEAD with the following terms of reference:

"To consider whether, having regard to recent developments in medicine, there are any fresh fields where health education might be expected to be of benefit to the public; how far it is possible to assess the results of health education in the past; and in the light of these considerations what methods are likely to be most effective in future." Medical members of the committee are Professor R. V. BRADLAW, Dr. H. D. CHALKE, Dr. S. WAND, Dr. J. T. BALDWIN, Professor G. R. HARGREAVES, Professor R. C. WOFINDEN.

Medical Fellows of the Royal Society

We regret the omission of the following name from the list published in the *Journal*, July 16 (p. 207):

1934

Lieutenant-Colonel R. B. SEYMOUR SEWELL, Indian Medical Service (retired), noted for his work as surgeon-naturalist to the Marine Survey of India, as director of the Zoological Survey of India, and as leader of the John Murray Expedition to the Indian Ocean. He is particularly distinguished for his oceanographical work.

Oliver Memorial Fund

Applications are invited for the Oliver Memorial Fund's award of £50 to a British subject whose original work or services in connexion with blood transfusion is considered to be a notable contribution to the research, organization, or donor aspect of this subject. Applications should be submitted before September 30 to the Honorary Secretary, Mrs. F. E. BEDBOROUGH, 105, New Park Avenue, London, N.13.

Institute of Laryngology and Otology

Mr. J. C. HOGG has succeeded Mr. C. GILL-CAREY as Dean.

Oxford University

Professor A. W. WILLIAMS, professor of medicine, Makerere College, University College of East Africa, has been appointed to the directorship of postgraduate medical studies at Oxford University.

Hammersmith Hospital

A new operating theatre suite, united to the two existing theatres, was opened at Hammersmith Hospital on July 12 by the Minister of Health, Mr. D. WALKER-SMITH. The suite includes a recovery ward which can take up to 10 patients.

Governors of Provincial Teaching Hospitals

The following are among those appointed to the Boards of Governors of provincial teaching hospitals:

United Newcastle upon Tyne Hospitals, Dr. S. W. Davidson, Professor A. G. R. Lowdon, Mr. Francis E. Stabler, Professor R. B. Green, Mr. F. McGuckin, Professor E. A. Pask, Dr. John S. Noble, Professor G. A. Smart, Dr. C. N. Armstrong. *United Leeds Hospitals,* Dr. H. G. Garland, Mr. A. B. Pain, Professor R. E. Tunbridge, Professor F. E. Hopper, Dr. E. W. Jackson, Professor P. J. Moir, Dr. J. E. Rushby, Dr. J. R. H. Towers, Colonel G. Armitage, Professor A. S. Johnstone. *United Sheffield Hospitals,* Mr. J. L. A. Grout, Professor John G. McCrie, Professor George I. Roberts, Professor Charles H. Stuart-Harris, Mr. R. B. Zachary, Dr. A. Jordan, Dr. Charles S. O'Flynn, Professor C. S. Russell, Mr. J. C. Anderson, Dr. I. B. Sneddon. *United Cambridge Hospitals,* Dr. Leslie B. Cole, Dr. Robert Ellis, Dr. D. M. T. Gairdner, Dr. R. I. N. Greaves, Professor J. S. Mitchell, Professor A. L. Banks, Dr. F. A. Grange, Dr. D. McC. Gregg, Mr. D. G. Bratherton, Mr. A. J. Rook. *United Oxford Hospitals,* Mr. P. R. Allison, Dr. G. S. Dawes, Mr. J. B. Pennybacker, Dr. J. Badenoch, Dr. A. H. T. Robb-Smith, Dr. Honor Smith, Dr. J. L. Boldero, Colonel L. K. Ledger, Mr. J. A. Stallworthy, Dr. H. R. Vickers, Dr. A. R. H. Williamson. *United Bristol Hospitals,* Dr. R. H. Butcher, Dr. A. P. Gorham, Professor C. B. Perry, Dr. G. E. F. Sutton, Professor A. I. Darling, Mr. H. D. Fairman, Professor R. J. Brocklehurst, Mr. C. A. Brown, Professor T. F. Hewer, Mr. R. E. Horton. *United Cardiff Hospitals,* Professor A. S. Duncan, Dr. A. Trevor Jones, Mr. R. G. Maliphant, Professor W. Woolf Mushin, Professor L. C. Rogers, Professor H. Scarborough, Dr. James Walker, Mr. H. R. S. Harley, Dr. L. H. Howells. *United Birmingham Hospitals,* Professor A. L. d'Abreu, Dr. A. Beauchamp, Dr. J. C. Heather, Professor T. McKeown, Professor Sir Arthur P. Thomson, Dr. A. B. Taylor, Dr. R. S. Aitken, Dr. E. Bulmer, Dr. C. G. Parsons, Dr. W. T. Cooke, Professor A. B. MacGregor. *United Manchester Hospitals,* Dr. W. Chadwick, Professor W. F. Gaisford, Dr. R. Wm. Luxton, Professor Sir Robert Platt, Professor W. Schlapp, Mr. H. T. Simmons, Dr. F. Janus, Professor G. A. G. Mitchell, Professor H. G. Radden, Dr. A. Morgan Jones, Professor W. I. C. Morris, Emeritus Professor Sir Harry Platt. *United Liverpool Hospitals,* Dr. G. R. Ellis, Mr. J. M. Leggate, Dr. E. L. Rubin, Mr. R. Selby, Lord Cohen of Birkenhead, Mr. C. J. K. Hamilton, Mr. J. B. Oldham, Dr. A. R. D. Adams, Professor C. A. Wells.

"The London Clinic Medical Journal"

The London Clinic, which has been run as a non-profit-making organization since the Trustees were appointed in 1936, has now launched its own journal, *The London Clinic Medical Journal*. Mr. RODNEY H. MAINGOT is the chairman of the editorial board, and the members of the board are Dr. F. AVERY JONES, Dr. J. W. D. BULL, Mr. T. G. REES, and Dr. ALFRED BYRNE.

The July issue includes articles on "The Scope of Plastic Surgery" by the late Sir ARCHIBALD MCINDOE, "Smoking and the Alimentary Tract" by Dr. F. AVERY JONES, "Traumatic

Progressive Encephalopathy of Boxers" by Dr. MACDONALD CRITCHLEY, "Viral Conjunctivitis" by Sir STEWART DUKE-ELDER, F.R.S., and "The Therapeutic Conquest of Malaria" by Sir PHILIP MANSON-BAHR. It is hoped that publication will be quarterly, at a cost of 2s. 6d. an issue. At present inquiries should be sent to the London Clinic, 20, Devonshire Place, London, W.1.

"Family Doctor"

The August issue of *Family Doctor* is now available, price 1s. 6d. Its contents include articles on immunization by Dr. A. WITHNELL, on spina bifida by Dr. J. N. WALTON, on swallowing foreign bodies by Mr. CLIFFORD BREWER, and on a snoring trial by Dr. HARVEY FLACK.

M.R.C.: Transfer of Unit

The Medical Research Council's Neuropsychiatric Research Unit, under the direction of Dr. D. RICHTER, has recently been transferred from the Whitchurch Hospital, Cardiff, to the Council's Laboratories at Carshalton, Surrey.

In Brief

India's family planning centres will be increased from 1,800 to 8,200, according to her third five-year plan which begins next year. It is estimated that her population by 1966 will be 480 millions.

People in the News

Dr. MORRIS FISHBEIN, formerly editor of the *Journal of the American Medical Association* and well known as a writer on medical subjects, celebrated his 71st birthday on July 22 with a dinner at Claridge's Hotel which was attended by many eminent in the world of science and medicine, including Mr. BASIL O'CONNOR and Sir GEOFFREY MARSHALL, who last week jointly presided over the International Conference on Congenital Malformations, sponsored by the National Foundation (U.S.A.) (see p. 376). In an informal after-dinner speech Mr. O'Connor paid a charming tribute to Dr. Fishbein's wife, Mrs. Anna Fishbein.

Professor Sir AUBREY LEWIS is to serve on the advisory council of the Institute of Criminology, Cambridge.

Dr. A. J. AMOR has been appointed medical adviser to the London Electricity Board.

Dr. J. P. QUILLIAM has been appointed a member of the General Optical Council, being a medical practitioner concerned with the instruction of pre-clinical students.

COMING EVENTS

97th British Pharmaceutical Conference. — Newcastle, September 5–9. Chairman, Professor W. H. LINNELL (dean, School of Pharmacy, University of London), whose address is entitled "Academic Research and the Five Freedoms." Papers will be read on subjects connected with research in the manufacture, analysis, testing, storage, and administration of a number of drugs. Details from the Conference Secretariat, 17, Bloomsbury Square, London, W.C.1.

West End Hospital for Neurology and Neurosurgery.—Clinical demonstrations in neurology open to medical practitioners and medical students, Tuesdays at 5.30 p.m., September 13 to December 13. Details from Secretary of Medical School, 91, Dean Street, London, W.1.

Chartered Society of Physiotherapy.—Annual congress, September 15, 16, 17, Assembly Rooms, St. Pancras Town Hall, London, N.W.1. Medical practitioners welcome. Programme and admission tickets from the Society's Secretary, Tavistock House (South), Tavistock Square, London, W.C.1.

"Accident Management and General Practice."—Joint symposium: British Orthopaedic Association, College of General Practitioners, and Institute of Accident Surgery at the Medical School, Birmingham University, September 24, 25. Sessions include: "The Accident Problem," "Major Injuries," "Minor Injuries," and "Burns." Details from Dr. C. M. GREEN, 8, Albert Road, Harborne, Birmingham, 17.

Institute of Dermatology.—One-day course in dermatology for medical registrars, September 29. Applications to the Dean of the Institute, St. John's Hospital for Diseases of the Skin, Lisle Street, London, W.C.2, by August 31.

1st International Symposium of Cybernetic Medicine.—Naples, October 2–4: "The Introduction of Cybernetic Methods in Modern Medicine." Details from the Secretariat, 348, Via Roma, Naples, Italy.

NEW ISSUES

GUT

Crohn's Disease (Regional Enteritis) of the Large Intestine and its Distinction from Ulcerative Colitis. H. E. Lockhart-Mummery and B. C. Morson.
Volvulus of the Caecum. Geoffrey Chamberlain.
A Test of Pancreatic Function in Man Based on the Analysis of Duodenal Contents after Administration of Secretin and Pancreozymin. P. Burton, D. G. Evans, A. A. Harper, Henry T. Howat, S. Oleesky, J. E. Scott, and H. Varley.
Serum Amylase and Serum Lipase Levels in Man after Administration of Secretin and Pancreozymin. P. Burton, Elizabeth M. Hammond, A. A. Harper, Henry T. Howat, J. E. Scott, and H. Varley.
Leucine Aminopeptidase with Special Reference to Ulcerative Colitis. L. J. Witts and S. W. Perry.
Effect of Glucagon on Gastric Secretion in Man. A. G. Melrose.
Effect of Glucagon on Gastric Secretion in the Dog. S. D. Clarke, D. W. Neill, and R. B. Welbourn.
Partial Gastrectomy for Peptic Ulcer. V. S. Brookes, J. A. H. Waterhouse, and P. A. Thorn.
A Report of Two Cases of Whipple's Disease Diagnosed by Peroral Small Intestinal Biopsy. C. J. Dickinson, M. Hartog, and Margot Shiner.
Hepatic Necrosis Due to Marsilid. C. F. McCarthy and M. R. Sheridan.
Smoking and the Alimentary Tract: A Review. R. S. Packard.
Present-day Techniques:
Use of Bisacodyl in Preparation of the Bowels for a Barium Enema. J. G. Sowerbutts.
Gastro-intestinal Blood Loss Measured by Radioactive Chromium. A. D. Cameron.

Volume 1, No. 2. (Quarterly; £3 annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

Clinical and Experimental Study of the Basal Membrane of the Corneal Epithelium in Keratitis Bullosa. J. Forgacs.
Ocular Aspects of Electromyography. S. I. Davidson.
Vitamin Deficiencies in Relation to the Eye. Mekki el Sheikh.
Effect of Neptazane on Intra-ocular Pressure in Relation to its Systemic Action and its Clinical Application. D. A. Campbell.
Electroretinography in Congenital Dyschromatopsia. J. François, G. Verriest, and A. de Rouck.
New Method for Correction of Entropion with Trichiasis by Tarsotomy. K. G. Hadija.
Acute Myeloid Leukaemia with Leukaemic Deposit in the Orbit. B. M. Chatterjee and N. N. Sen.
Reviews. Notes. Obituary.

Volume 44, No. 7. (Monthly; £6 annually. With *Ophthalmic Literature* and Index, £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, August 5

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Howard Nicholson: clinical demonstration.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gale.—On July 12, 1960, at Liverpool Maternity Hospital, to Gillian Margaret (formerly Whitaker), wife of Dr. David Gale, a daughter—Jennifer Mary.
McCallum.—On July 8, 1960, at Nottingham, to Dr. and Mrs. D. I. McCallum (formerly Dr. Isabel S. Smellie) a daughter.
Rabett.—On July 20, 1960, at the Central Middlesex Hospital, London, N.W., to Jane (formerly Straight), wife of Dr. Robert J. Rabett, a daughter.
Sutherland.—On July 17, 1960, at Talbot Lodge, Lifton, Devon, to Mary (formerly Carlile), and Charles M. Sutherland, a daughter—Alison Mary.

DEATHS

Brown.—On June 16, 1960, at Cottage Hospital, Marlow, Edward Middleton Brown, M.D., formerly of Tring, Herts.
Fox.—On June 22, 1960, the result of an accident, John William Fox, M.B., D.P.H. of Yew Dene, Leeds, Kent, aged 81.
Halsted.—On June 18, 1960, at Clavadell, Belmont, Surrey, Denis Gratwicke Halsted, M.B., aged 95.
Hunt.—On June 19, 1960, Sydney Hunt, M.R.C.S., L.R.C.P., of Spondon, Derby, aged 84.
Scorgie.—On June 18, 1960, John Scorgie, M.B., Ch.B., aged 43.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Milroy's Disease

Q.—*What are the latest views on the aetiology, pathology, and treatment of Milroy's disease (chronic oedema of legs)?*

A.—The term Milroy's disease must be confined to those cases of familial and hereditary oedema of the legs which are present at birth or shortly afterwards or occasionally develop some years later. The cause of the condition is unknown, the disease is inherited as a Mendelian dominant, and, since there is no pathological evidence of abnormality in the subepithelial lymphatics, it must be regarded as due to some inborn deficiency in their absorbing power.

The lymph stasis initiates a train of pathological processes leading to aggravation of the local condition. The prolonged lymphatic obstruction causes incompetence of lymph valves, the protein content of the retained fluid is high, and the tissues are prone to recurrent attacks of lymphangitis which are followed by progressive fibrosis of the subcutaneous tissues and irreversible damage to the lymphatic endothelium. In this way a vicious circle is established which may ultimately lead to elephantiasis and secondary skin changes.

Treatment is often ineffective, but symptomatic relief is possible. This includes permanent bandaging with strong elastic or rubber bandages, the use of bed blocks at the lower end of the bed, and the limitation of standing and of sitting with the legs dependent. Surgical treatment is often advisable owing to the progress of the disease, the size of the limbs, and the degree of discomfort. Operations fall into four main groups. First, there are those which remove part of the redundant tissue. Secondly, those of the Kondoleon type or its modifications, which remove much of the redundant tissue together with the underlying deep fascia, and thus establish drainage connexions between the subcutaneous and the subaponeurotic lymphatic systems. Thirdly, there are those plastic operations designed to bring a lymphatic-bearing bridge of skin across the obstruction region and so assist drainage. Finally, there are the more recent types of operation in which all the subcutaneous tissues are removed from the leg and the flayed organ covered either with free-skin grafts or by replacing the patient's skin to the thickness of Wolfe's grafts. Most of these operations are difficult and time-consuming, but they may be helpful in relieving some of the disability in the worst cases.

During the past few years there have been encouraging reports of the use of cortisone[1] and prednisone[2] before irreversible changes have developed.

REFERENCES

[1] Drinker, S. J., and Gottfries, I., *Acta med. scand.*, 1954, **150**, 277.
[2] Panos, T. G., *J. Amer. med. Ass.*, 1956, **161**, 1475.

Familial Hyperbilirubinaemia

Q.—*What is familial hyperbilirubinaemia? What is the prognosis, and does it contraindicate work in the Tropics or Middle East?*

A.—When the serum bilirubin level is measured in a large number of apparently healthy individuals, a certain proportion will be found above the normally accepted upper limit of 1 mg. per 100 ml. In some instances this will be due to a haemolytic process and in others to such conditions as cirrhosis of the liver. There remain a few people in whom the serum bilirubin level is raised in the absence of haemolytic or of hepatocellular disease. These patients are suffering from harmless congenital defects in bilirubin metabolism, termed "familial hyperbilirubinaemias."[1] These are often diagnosed in doctors, medical students, or nurses, who tend to be more aware of their complexions and who may be having their serum bilirubin levels estimated for some other reason. The patients are either symptomless or else complain of intermittent nausea and malaise. The conditions are familial and are inherited as dominants. The usual variety is the Gilbert type.[2] Serum bilirubin levels rarely exceed 5 mg. per 100 ml.; other biochemical tests of liver function are normal. Cholecystogram and liver biopsy are also normal. In the Dubin–Johnson–Sprinz type[3] serum alkaline phosphatase may also be elevated, cholecystography shows a non-functioning gall-bladder, and the liver cells, on biopsy, are full of a dark brown pigment, "black liver jaundice." Recently a similar type has been described but without the brown pigment in the liver cells.[1] These familial non-haemolytic hyperbilirubinaemias are associated with normal life expectancy and do not contraindicate work in the Tropics or Middle East.

REFERENCES

[1] Schiff, L., and Billing, B. H., *Gastroenterology*, 1959, **37**, 595.
[2] Foulk, W. T., Butt, H. R., Owen, C. A., jun., Whitcomb, F. F., jun., and Mason, H. L., *Medicine (Baltimore)*, 1959, **38**, 25.
[3] Dubin, I. N., *Amer. J. Med.*, 1958, **24**, 268.

Zonulysis in Lens Extraction

Q.—*What is the new zonulysis treatment for cataract, originating in Barcelona? Where may it be carried out?*

A.—In 1957 J. Barraquer, of Barcelona, discovered that the enzyme alpha-chymotrypsin would act on the zonule of the lens when introduced into the anterior chamber. The attachment of the zonular fibres to the lens is broken down by the enzyme so that mechanical rupture of the zonule during intracapsular extraction is unnecessary, and removal of the lens is facilitated. This is particularly valuable in young patients, in whom the zonule is stronger than in the elderly, but most surgeons feel that it is contraindicated for congenital cataract. After zonulysis the dislocated lens is best removed by an erisyphake, but otherwise the technique is similar to that commonly used in intracapsular extraction and is within the competence of any ophthalmic surgeon. Complications such as striate keratitis with vascularization, loss of vitreous, and retinal detachment have been reported. In the writer's opinion the slightly increased risk involved does not warrant the use of alpha-chymotrypsin in the routine surgery of senile cataract.

Risks of Hair-dyeing

Q.—*What dangers arise from the use of permanent hair dyes?*

A.—The main danger from the permanent hair dyes in present-day use is the development of allergic epidermal hypersensitivity to the dye. Paraphenylenediamine is the most well known of these, and is very apt to cause hypersensitive reactions. Others, such as paratoluylenediamine, are claimed to be less troublesome in this respect, but are by no means free from risk. The occurrence of a severe dermatitis can be largely avoided if a patch test of the dye is made on the skin 48 hours before the dyeing is to be carried out. Such a test will give an allergic eczematous response if the skin is sensitive, and, if it is, the dyeing should on no account be carried out.

Any trained hairdresser knows about this test, but it is very frequently neglected, and many hairdressers appear to think that if the test is carried out once and is negative it need never be done again. This type of sensitivity is, of course, acquired by previous contact, so that it is essential for the test to be made every time the dyeing is carried out.

There seems to be an increasing tendency for hairdressers to bleach the hair before dyeing. When this is carried out with proper care no great damage results, though the hair may become rather harsh to the touch. If, however, the bleaching process is too vigorous the hair becomes brittle

and a good deal of hair may thus be lost. Brittleness of the hair produced in this way is likely to be made worse by permanent waving, and occurs chiefly in subjects with fine, fair, or silky hair.

Efficacy of B.C.G. Vaccination

Q.—*What are the chances of infection in those who have (1) a positive Mantoux reaction, and (2) a negative Mantoux reaction when in frequent contact with tuberculous patients with positive sputum?*

A.—This question was answered by the report of the Prophit Tuberculosis Survey.[1] In this survey 10,000 young people, who were apparently healthy on entry, were examined and re-examined by tuberculin test and *x*-ray over a number of years. The tuberculosis morbidity rate was 7.3 in tuberculin-positive individuals and 23.1 in the tuberculin-negative. Both these figures were higher when there was evidence of repeated contact with tuberculosis. When such contact is known to exist there is now the strongest possible argument for B.C.G. vaccination of Mantoux-negative individuals.

REFERENCE

[1] Report of the Royal College of Physicians on the Prophit Tuberculosis Survey, 1935-1944, *Tuberculosis in Young Adults*, 1948. H. K. Lewis, London.

Fitness for Local Authority Employment

Q.—*Is it correct to reject a candidate for a local authority's superannuation scheme who has severe bilateral varicose veins of the legs? If rejected, could he be certified medically as a handicapped person?*

A.—There is no statutory requirement that local government employees must be certified as medically fit before taking up an appointment, but nevertheless a great many local authorities require this to be done. Medical unfitness cannot prevent an employee from participating in the superannuation scheme if he is in fact appointed.

After completing his examination the doctor reports on the candidate's fitness as he considers best, but the following categories may be found useful: (1) Those who are in good health and free from any physical defect. (2) Those who are in good health but possess defects which are not likely to interfere with the duties for which the candidate is to be appointed. (3) Those whose condition is such—in the opinion of the examining doctor—as to make them medically unfit for entering the superannuation scheme.

In the case in question consideration should be given to the man's age, his past medical history, and the type of work he will be called upon to do—for example, prolonged standing would almost certainly be ruled out. A decision could then be made on whether he could be placed in category (2) above. Advice might also be given on the possibility of some form of treatment for the condition, but treatment to remove the disability cannot be insisted upon before taking up employment.

By "certifying medically as a handicapped person" the question presumably means eligibility for registration with the Ministry of Labour as a "disabled person" (Disabled Persons (Employment) Act, 1944). This would imply that he is substantially handicapped in obtaining or keeping his normal employment. Full information on this point can be obtained from the disablement resettlement officer (D.R.O.) at the local employment exchange.

Risks of Caesarean Section

Q.—*How much weight should be attached to a pregnant woman's request for delivery by caesarean section when there are no other indications for this mode of delivery?*

A.—It is reckoned[1] that the maternal mortality rate for caesarean section is seven times higher than that for all deliveries. The operation also involves hazards to immediate and future health and to subsequent child-bearing. It does not even guarantee a live birth, and there are statistics to show that elective caesarean section carries a *corrected* perinatal mortality rate of 2%. Such figures make it clear that there should always be a medical indication for the operation. In other words, there should always be good reason to believe that the operation offers better chances for the life and health of the mother or child than does vaginal delivery in the circumstances of a particular case. This does not mean that a psychological indication such as a genuinely abnormal and overpowering fear of labour might not exceptionally be admissible. Nevertheless, because of its added risk, caesarean section should not be performed merely because the patient requests it.

REFERENCE

[1] *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1952-1954*, 1957. Ministry of Health Report No. 97. H.M.S.O., London.

"Seed Corns"

Q.—*What is meant by the term "seed corn"?*

A.—I do not know what is meant by the term "seed corn." Seed warts is a popular term for one or more warts which appear in the neighbourhood of a single wart, presumably as the result of infection from the original wart. Seed warts are found most commonly on the hands or the soles.

NOTES AND COMMENTS

Intravenous Iron.—Dr. D. M. SOPHER (London, W.13) writes: In your reply ("Any Questions?" May 28, p. 1674) I was somewhat perturbed at your assertion that iron dextran complex was not suitable for intravenous use. At the persuasion of a representative of the manufacturers of "imferon" (Bengers) in June, 1958, we have since used this product intravenously fairly extensively in hospital practice. Using the same volume, imferon contains two and a half times the amount of iron in "ferrivenin," thus necessitating fewer injections. Taking the same precautions as we did for ferrivenin, we had no more frequent nor more severe reactions. I shall be grateful if you would let me know the authority on which you base this assertion. I myself have no more than the word of a representative of the manufacturers that it is safe to use imferon intravenously.

OUR EXPERT replies: I am aware that some have been using iron dextran complexes intravenously in the treatment of iron-deficiency anaemia, but originally the makers of these were not enthusiastic about its being used by this route because of the reactions that might occur, and certainly these preparations are not as safe nor as easy to give as the preparations specifically made for intravenous administration. I have, however, tried these iron dextran complexes intravenously in the past, and I was not happy about them because of the severe reactions that did occur far more frequently than when using the non-dextran preparations such as "neoferrum." The occurrence of these reactions, therefore, did not suggest that this was a safe and justifiable method of treatment.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Clinical Pathology in General Practice (22s. 3d.).
Any Questions?, Volume 3 (8s. 3d.).

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